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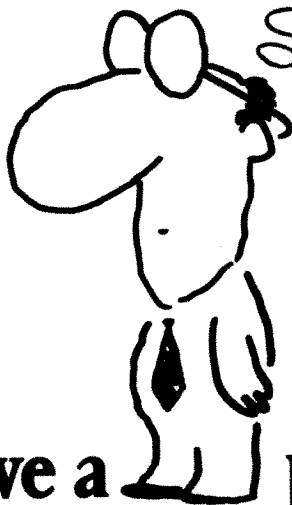
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1. Uzman, E. *et al.*, Am J Ophthalmol 1982; 94 (3): 318-327. 2. Rakofsky S.I. *et al.*, Ophthalmology 1989; 96 (1): 8-11.

3. Andel, T. *et al.*, Am J Ophthalmol 1986; 101: 298-304.



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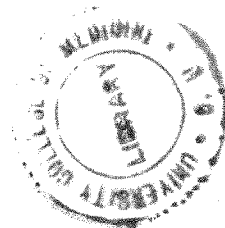
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BRITISH JOURNAL OF OPHTHALMOLOGY



Editorial

Diabetic retinopathy and cataract surgery

Two papers in the current issue, one from Pollack, Dotan, and Oliver of Israel and the other from Cunliffe and colleagues of Cambridge, deal with the effects of cataract surgery on diabetic retinopathy and its complications. All ophthalmologists are aware that there are possible extra hazards when cataract extraction has to be done in the presence of diabetic retinopathy, but in view of the fact that about 10% of cataract patients have diabetes, and that most of those whose diabetes is of fairly long duration are also likely to have retinopathy, it is surprising that in the ordinary course of events serious postoperative complications of the sort one might fear seem to happen so seldom. Galloping rubeosis and/or accelerated retinopathy ought to be almost everyday occurrences in busy cataract programmes, yet they do not appear to be.

There is no doubt that the postoperative visual prognosis of diabetics with retinopathy is worse than of those without, but that is only what one would expect. Perhaps a more important consideration is whether the retinopathy is itself exacerbated by the patient being rendered aphakic. If microvascular ischaemia is the primary event in diabetic retinopathy, with neovascularisation of retina and eventually iris to follow, what would be the most likely effect of aphakia? One would have thought that the freer movement of fluids between anterior and posterior segments, with a general tendency towards the anterior part of the eye, would shift the neovascularising stimulus (whatever it is) forwards. Rubeosis ought to be more likely and retinal neovascularisation less likely. There is indeed some evidence that the risk of rubeosis is increased by extraction,¹ but the evidence for a relative improvement in retinal neovascularisation does not seem to be forthcoming, and indeed one of the papers in the present issue indicates the exact opposite. It is even suggested that the increase of neovascularisation which is said to occur might be directly due to the absence of the lens, which is thought normally to contribute a component to the anti side of the pro-anti neovascularisation balance thought to exist in the normal eye. That there is evidence for an antineovascularising factor in the lens is not disputed (the matter is referenced in the paper by Pollack *et al.*), but it is only one component in what is probably a complex interplay of factors and seems unlikely to play a major role in view of the large

numbers of diabetic cataracts which are extracted without trouble.

One would not be surprised if factors tending to discourage vascular endothelial cell proliferation were not to be found in most normally avascular tissues of the body as part of their own defences against vascularisation, and so far as the eye is concerned this would mean the lens, the vitreous, and the cornea. Antineovascularising substances have been suggested in the first two but not I believe in the third. It is of some interest, however, that some of the original work involved in the search for neovascularising substances was carried out in corneal pockets, and one wonders whether, if the cornea itself is not such a passive vehicle for the test tissues and substances as researchers assumed, the results of such experiments may have been modified by the substrate in which they were performed.

Kissun and Garner,² for example, failed to induce neovascularisation in experimental corneal tunnels by implants of extracts of ischaemic kitten retina. They themselves pointed out that 'local factors, such as may well be involved in using the cornea as a substrate,' might be better avoided by some other form of testing being devised. So far as laboratory work is concerned, tissue culture experiments with media conditioned by various tissue extracts and other substances would appear to be less susceptible to confounding influences than in-vivo experiments on the cornea, and we await with interest further work on this fundamental aspect of ocular pathology. Publication of the recent Cambridge symposium, which dealt with some of the issues involved, may throw some more light on the matter.

Both papers in this issue offer some consolation for clinicians, since they provide evidence, one intentionally and the other involuntarily, that if a cataract extraction does have to be done for a patient with retinopathy the implantation of an intraocular lens is unlikely to constitute an additional hazard.

REDMOND SMITH

1 Aiello LM, Wand M, Liang G. Neovascular glaucoma and vitreous haemorrhage following cataract surgery in patients with diabetes mellitus. *Ophthalmology* 1983; 90: 814-20.

2 Kissun RD, Garner A. Vasoformative properties of normal and hypoxic retinal tissue. *Br J Ophthalmol* 1977; 61: 394-8.

ORIGINAL ARTICLES

Course of diabetic retinopathy following cataract surgery

Ayala Pollack, Shlomo Dotan, Moshe Oliver

Abstract

Five patients with mild to moderate retinopathy to both eyes underwent complication-free cataract surgery in one eye. Within three months of surgery deterioration of the retinopathy was observed in the operated eye only. In four patients there was an increase of intraretinal haemorrhages and hard exudates, accompanied by clinically significant macular oedema manifested as retinal thickening and extensive fluorescein leakage from both the macular and the peripapillary capillary networks. Of these four patients one also developed retinal ischaemia, evident ophthalmoscopically by flame-shaped haemorrhages and cotton-wool spots and angiographically by areas of capillary non-perfusion. The fifth patient showed proliferation of new blood vessels and vitreous haemorrhage. Diabetic patients scheduled for cataract surgery should undergo a thorough preoperative evaluation of any existing retinopathy. Postoperatively they should be followed up at close intervals so that any progression of retinopathy can be promptly detected and considered for laser treatment.

In diabetic patients without diabetic retinopathy visual acuity after cataract surgery is generally favourable and similar to that of non-diabetic patients.¹⁻⁵ However, if diabetic retinopathy is present at the time of surgery the prognosis may

be much worse.^{1-5,6} Jaffe and Burton⁷ described six patients with diabetic retinopathy who developed severe exudative macular oedema after cataract surgery, with poor final visual acuity. There was no progression of diabetic retinopathy in the non-operated fellow eye. We also have observed a rapid deterioration of diabetic retinal changes shortly after cataract extraction. Five representative cases are described in this report.

Case reports

CASE 1

A 75-year-old man was referred to our department for cataract surgery. He had an 11-year history of orally controlled diabetes mellitus and hypertension controlled by hypotensive medication. The findings on physical examination were normal. His visual acuity was finger counting in the right eye and 20/70 in the left. Applanation tonometry revealed normal intraocular pressure in both eyes. Slit-lamp examination showed a mature cataract in the right eye and progressive nuclear sclerosis in the left eye. Lens opacity of the right eye precluded fundal examination. Diabetic retinopathy, consisting of a few intraretinal haemorrhages and minute hard exudates, was observed in the left eye.

An uncomplicated intracapsular cataract extraction in the right eye was performed. Fundal examination on the day after surgery

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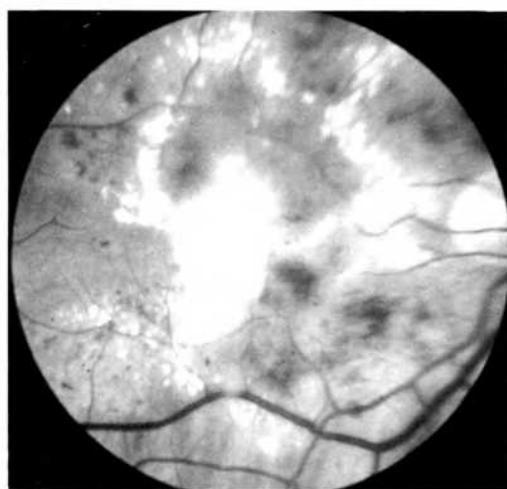


Figure 1A

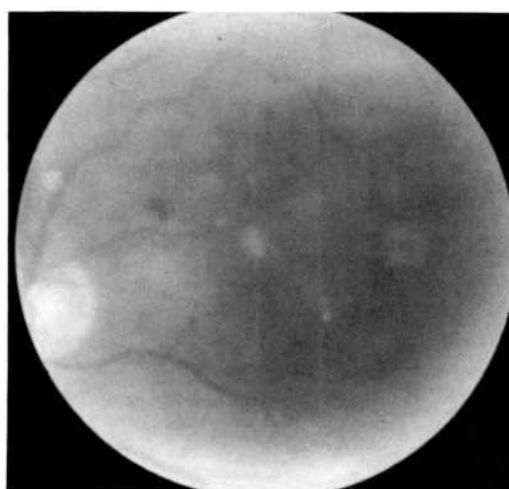


Figure 1B

Figure 1 Case 1. A: Ophthalmoscopic appearance of the right eye one month after surgery. Dot and flame shaped haemorrhages are present, and a ring of hard exudates extends to the fovea and surrounds an area of retinal thickening. B: Ophthalmoscopic appearance of the left non-operated cataractous eye on the same day shows mild diabetic retinopathy consisting of a few haemorrhages.

revealed a few small intraretinal haemorrhages in the posterior pole. Over the next two weeks he developed cystoid macular oedema. Visual acuity was 20/200.

After one month, the visual acuity in the operated eye had deteriorated to finger counting. Fundal examination disclosed aggravation of the pre-existing diabetic retinopathy, with diffuse macular oedema and a marked increase of the intraretinal haemorrhages and hard exudates. The latter now formed a dense ring adjacent to the superior vascular arcade and extended to the fovea (Fig 1A). At the same time the non-operated left eye had remained stable (Fig 1B). Fluorescein angiography showed extensive leakage of dye in the posterior pole of the operated eye and only a small focus of leakage corresponding to the area of hard exudates in the fellow eye.

Grid argon laser photocoagulation was applied to the right eye. Examinations over the next few months revealed a gradual absorption of the hard exudates and formation of a foveal scar. Visual acuity one year after cataract extraction was 20/200.

The retina of the unoperated eye appeared stable over a follow-up period of two years; however, the cataract progressed and the vision declined to 20/200. A few dot haemorrhages and hard exudates were noted in the retina. In view of the postoperative deterioration of the diabetic retinopathy in the right eye focal argon laser photocoagulation was recommended for the left eye. However, because of opacities in the lens the treatment could not be completed, and the patient underwent an uneventful extracapsular cataract extraction in the left eye. Fundal examination on the day after surgery revealed diabetic retinopathy with a few dot and flame-shaped haemorrhages and minute hard exudates. Three months after surgery the amount of hard exudates and macular oedema had increased significantly, and grid argon laser photocoagulation was performed. The visual acuity 20/200. The macula showed atrophic changes, which were probably related to the resolved postoperative macular oedema.

CASE 2

A 78-year-old woman with a 20-year history of insulin-dependent diabetes mellitus was referred to our department for cataract surgery. One year earlier she had undergone argon laser

iridotomies in both eyes for narrow angle glaucoma. The intraocular pressure in both eyes was controlled without medication. Visual acuity was finger counting in the right eye and 20/70 in the left. Slit-lamp examination revealed patent iridotomies in both eyes, progressive nuclear sclerosis in the right eye, and mild nuclear sclerosis in the left eye. The fundus of the right eye could not be seen because of lens opacities. The left eye showed diabetic retinopathy, consisting of a few small dot haemorrhages.

An uncomplicated extracapsular cataract extraction with posterior chamber intraocular lens implantation was performed in the right eye. Fundal examination of the right operated eye on the day after surgery showed diabetic retinopathy, similar to that in the left eye, consisting of a few dot haemorrhages and microaneurysms. The vision improved to 20/40. Three months after surgery the visual acuity in the right eye had declined to 20/70 while remaining unchanged in the left eye. Fundal examination of the operated eye showed diffuse retinal thickening in the macular area with superimposed cystoid macular oedema. Fluorescein angiography of that eye during the early arteriovenous phase showed numerous prominent microaneurysms and dilatation of the capillary bed in the entire posterior pole as well as in the peripapillary capillary network. Late angiograms showed extensive fluorescein leakage in the entire posterior pole, extending from the peripapillary area towards the vascular arcade. Superimposed perifoveal cystoid macular oedema was also noted (Fig 2A). Although fluorescein angiography of the left eye also disclosed foci of dye leakage in the posterior pole, it was not as prominent as in the operated eye and did not extend beyond the vascular arcades (Fig 2B). Grid argon laser photocoagulation was applied in the right eye because of the clinically significant macular oedema seen on ophthalmoscopy and the extensive fluorescein leakage observed in the entire posterior pole. The oedema subsequently resolved and the vision improved to 20/30.

CASE 3

A 70-year-old man with a 20-year history of orally controlled diabetes mellitus was referred to our department for cataract surgery. His medical history included cholecystectomy for acute cholecystitis one year earlier. The visual

Figure 2 Case 2. A: Late arteriovenous phase of fluorescein angiography three months after surgery in the right eye shows diffuse leakage at the posterior pole extending beyond the vascular arcades and to the peripapillary region. B: Fluorescein angiography of the left cataractous eye shows significantly fewer foci of less intense leakage.

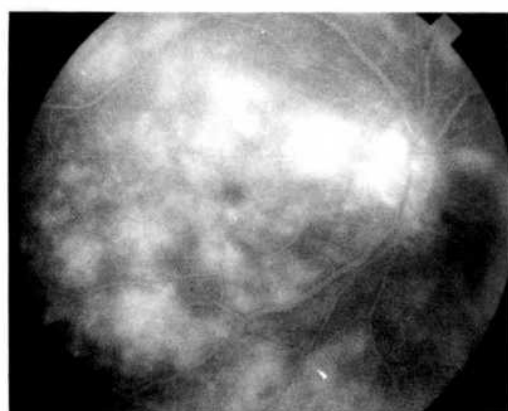


Figure 2A

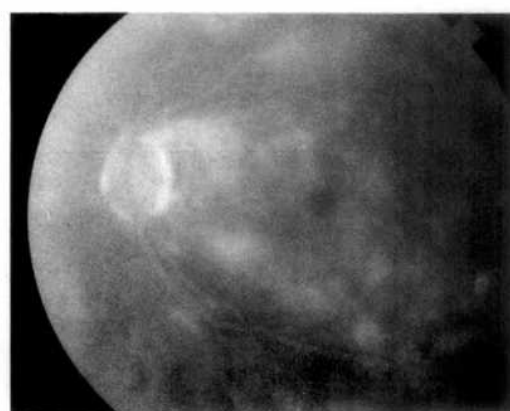


Figure 2B

Figure 3 Case 3. A: Preoperative late phase of angiogram shows a few microaneurysms (small arrow) and leakage adjacent to vascular arcades (long arrows). **B:** Postoperative late angiogram shows extensive leakage at the posterior pole and superimposed cystoid macular oedema. **C:** Late angiogram of the non-operated eye at that time shows microaneurysms and mild leakage.

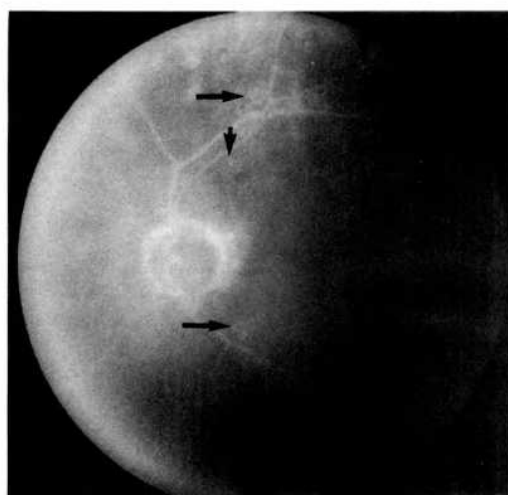


Figure 3A

acuity was 20/40 in the right eye and 20/200 in the left. Applanation tonometry revealed normal intraocular pressure in both eyes. Slit-lamp examination disclosed minimal nuclear sclerosis in the right eye and progressive nuclear sclerosis in the left. In both eyes funduscopy showed mild diabetic retinopathy consisting of microaneurysms and a few small dot haemorrhages. Preoperative fluorescein angiography of the left eye showed a few microaneurysms and mild dye leakage adjacent to the vascular arcades (Fig 3A). The patient underwent an uncomplicated extracapsular cataract extraction in the left eye. Fundal examination of the operated eye immediately after surgery disclosed a few microaneurysms and small dot haemorrhages. Six weeks later funduscopy of that eye revealed cystoid macular oedema. Fluorescein angiography revealed multiple foci of dye leakage in the entire posterior pole including the peripapillary area, with superimposed cystoid macular oedema (Fig 3B). At the same time the non-operated eye showed a few microaneurysms and mild fluorescein leakage (Fig 3C). Visual acuity was 20/40 in both eyes. Since ophthalmoscopy the oedema in the operated eye has been very mild and the vision showed a tendency to improve, laser treatment was deferred, and the patient was put on indomethacin drops. Three months after surgery the macular oedema had resolved, and the final visual acuity of 20/40 has remained stable since that time.

CASE 4

A 63-year-old man was referred for cataract extraction. His medical history revealed diabetic neuropathy of the posterior tibial nerve in the right leg. His vision was 20/40 in the right eye and finger counting in the left. Intraocular pressure was normal. Slit-lamp examination showed mild cataract in the right eye and progressive cataract in the left. Fundal examination of the right eye disclosed diabetic retinopathy consisting of microaneurysms and dot and flame shaped haemorrhages. Although the left fundus could not be clearly visualised because of the cataract, it was possible to detect diabetic retinopathy, which appeared to be of similar severity to that in the right eye.

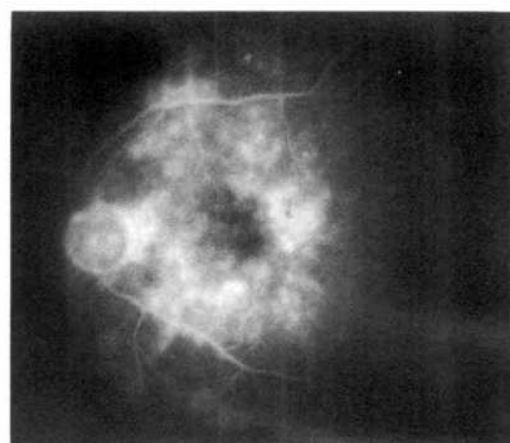


Figure 3B

The patient underwent an uncomplicated extracapsular cataract extraction with intraocular lens implantation in the left eye. Two months after surgery funduscopy of the operated eye revealed cystoid macular oedema, his vision declined from 20/40 to 20/70, and laser treatment was considered. However, it was three months before the patient again presented himself for follow-up examination, and by that time the vision in the left eye had improved to 20/40. Although ophthalmoscopy indicated that the clinical oedema had resolved, angiography disclosed persistent cystoid macular oedema. A year and a half after the operation the cataract in the unoperated right eye had progressed, and he was again scheduled for surgery. Although the fundus could be only vaguely visualised preoperatively, it was possible to observe diabetic retinopathy consisting of haemorrhages (Fig 4, top left). The patient underwent extracapsular cataract extraction with implantation of an intraocular lens in the right eye. One month after surgery funduscopy revealed an increased number of haemorrhages and minute hard exudates, a few cotton-wool exudates, and cystoid macular oedema (Fig 4, top right). Fluorescein angiography of the operated eye revealed dye leakage in the entire posterior pole extending to the vascular arcades. At the peripheral retina non-perfused areas were also

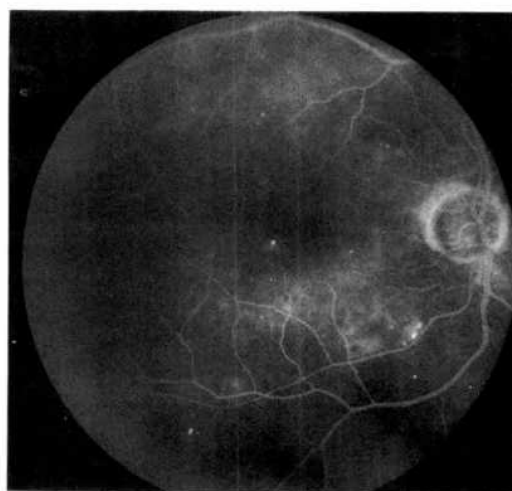
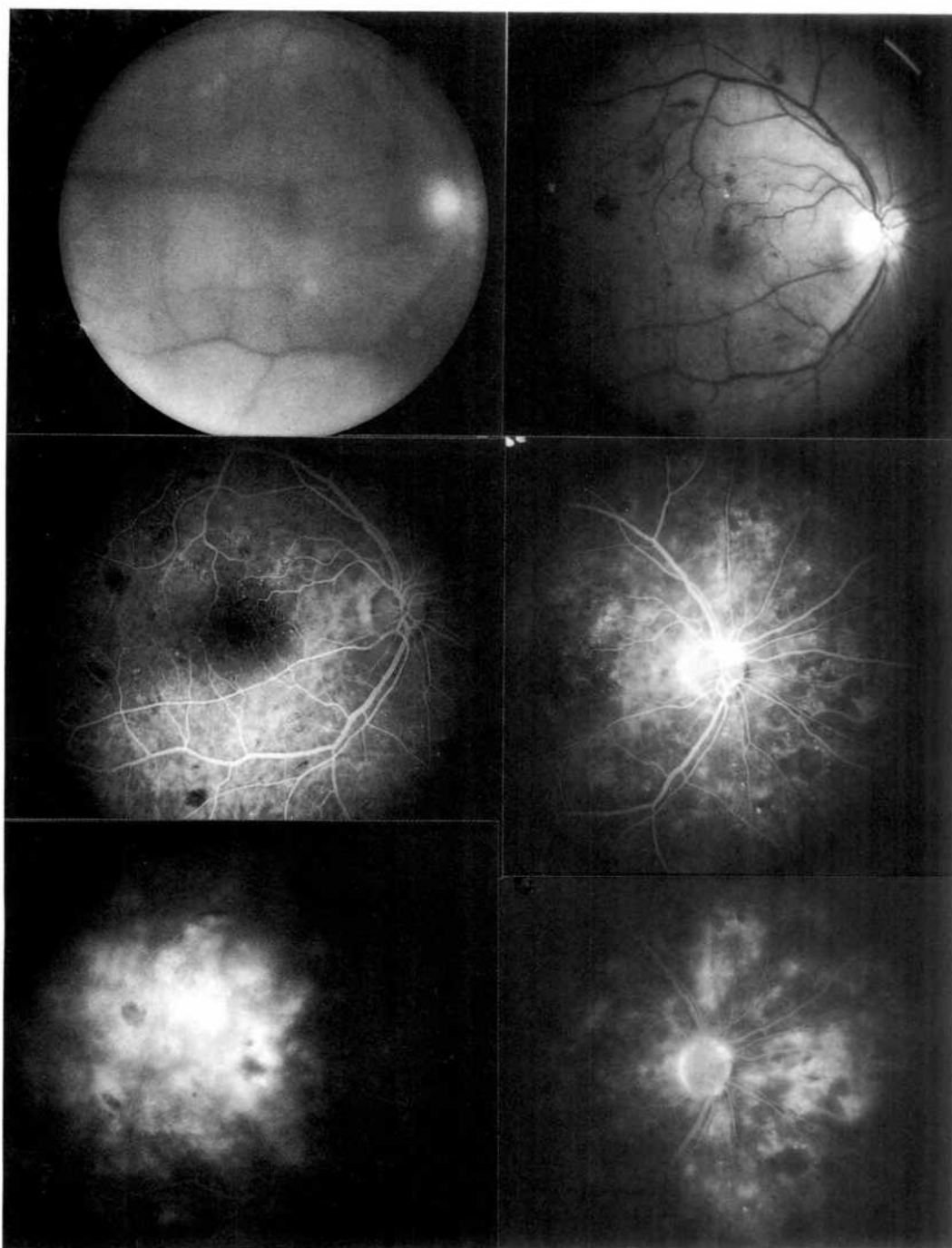


Figure 3C

Figure 4 Case 4. Top left: Preoperative ophthalmoscopic appearance of the right eye, showing the presence of haemorrhages. Top right: Postoperative preangiographic picture shows microaneurysms, numerous dot and flame shaped haemorrhages and minute hard exudates. Centre left: Angiogram of the early arteriovenous phase shows areas of blocked fluorescence corresponding to haemorrhages and numerous microaneurysms. Centre right: Mid-arteriovenous phase shows dye leakage from microaneurysms and dilated capillaries, as well as peripheral areas of capillary non-perfusion. Bottom left: Late phase angiogram shows extensive leakage over the entire posterior pole, with superimposed macular oedema. Bottom right: Late phase angiogram at the peripapillary area shows non-perfused areas surrounded by foci of fluorescein leakage.



observed (Fig 4, centre, bottom). Visual acuity was 20/30. Because of the good vision in this eye, as well as the spontaneous resolution of the macular oedema and the final good visual results in the previously operated eye, laser treatment was deferred, and the patient was followed up closely. Three months later the macular oedema had resolved. Two years after surgery his vision was 20/30, there was no clinical macular oedema, and the areas of retinal ischemia had not progressed.

CASE 5

A 71-year-old man was referred for cataract extraction. His visual acuity was finger counting in the right eye and 20/50 in the left. Slit-lamp examination showed progressive cataract in the right eye and mild nuclear sclerosis in the left eye. Funduscopy through the cataracts revealed

similar bilateral diabetic retinopathy with multiple dot haemorrhages, microaneurysms, and dilated veins. However, the left eye could be more clearly visualised than the right, and early new vessels were noted to come off the top edge of the optic disc.

An uneventful intracapsular cataract extraction was performed in the right eye. Fundal examination one week later disclosed numerous flame shaped haemorrhages and some soft exudates. One month after surgery proliferative diabetic retinopathy and vitreous haemorrhage were noted. The fundal appearance of the non-operated eye had remained unchanged (Fig 5A). Once the vitreous haemorrhage in the operated eye had partially cleared and the retina was visible, it was possible to discern disc neovascularisation, flame shaped haemorrhages, and soft and hard exudates in the posterior pole (Fig 5B). Argon laser panretinal photocoagulation was

Figure 5: Case 5. A: Ophthalmoscopic appearance of the right eye three months after cataract surgery, showing vitreous haemorrhage and disc neovascularisation. B: Ophthalmoscopic appearance of the left non-operated eye at the same time shows small haemorrhages and suspected early new vessels coming off the top edge of the optic disc.



Figure 5A

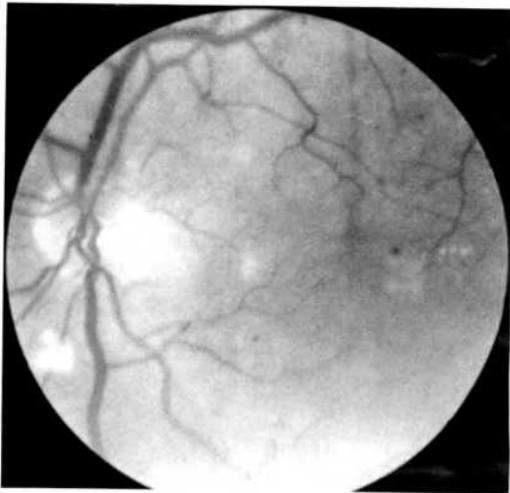


Figure 5B

performed. The final visual acuity was 20/200. Over the next three years there were no further retinal changes in the non-operated fellow eye. However, a follow-up examination three years later disclosed progression of the proliferative diabetic retinopathy in that eye. Panretinal photocoagulation was therefore performed, and the new blood vessels subsequently regressed. Six years after cataract extraction in the right eye the vision in the left eye had deteriorated to finger counting, and extracapsular cataract extraction with intraocular lens implantation was performed. No postoperative progression of the diabetic retinopathy was observed during the following year. The final visual acuity in that eye was 20/50.

Discussion

All five patients described in this report experienced rapid deterioration of diabetic retinopathy shortly after cataract surgery, resulting in asymmetric severity of the disease in the two

eyes. In the first four cases the deterioration was manifested by the increased number of dot and flame shaped haemorrhages and hard exudates and by the appearance of retinal oedema, marked retinal thickening, and cystoid macular oedema. Fluorescein angiography of the affected eyes showed diffuse leakage in the entire macular area with superimposed cystoid macular oedema, as well as leakage from the peripapillary capillary networks. Severe extensive macular oedema occurring after cataract surgery was reported also by Jaffe and Burton.⁷ In our series, however, cases 4 and 5 also developed retinal ischaemia, which was manifested ophthalmoscopically by preproliferative signs such as flame shaped haemorrhages and soft exudates, and angiographically by areas of capillary non-perfusion. In the fifth patient the ischaemic changes were more severe and consisted of neovascularisation and vitreous haemorrhage. In summary, the postoperative deterioration of diabetic retinopathy in these patients included vascular hyperpermeability and leakage as well as capillary

Table 1 Clinical findings before and after cataract surgery

Case no.	Diabetes			Other diseases		Visual acuity				Type of surgery	Status of DR		Treatment	
	Age (yr and sex)	Duration (yr)	Treatment			Pre-op.	Post-op.	Follow-up	Final		At op.	Post-op.	A-L	Others
1	75/M	11	Oral	Hypertension	—	CF	20/200	CF	20/200	ICCE	Dot haemorrhages Hard exudates	Dot + flame haemorrhages Massive exudates, ME, CME	Post-operative Grid	
	77/M	13	Oral	Hypertension	—	CF	20/200	20/200	20/200	ECCE+IOL	Dot haemorrhages Hard exudates	Dot + flame haemorrhages Massive exudates, ME, CME	Post-operative Grid	
2	78/F	20	Insulin	—	NAG ALI	CF	20/40	20/70	20/30	ECCE+IOL	Microaneurysms Dot haemorrhages	ME, CME	Post-operative Grid	
3	70/M	20	Oral	Cholecystectomy	—	20/200	20/40	20/40	20/40	ECCE+IOL	Microaneurysms Dot haemorrhages	ME, CME		Indomethacin drops
4	63/M	9	Oral	Diabetic neuropathy	—	CF	20/40	20/70	20/40	ECCE+IOL	Microaneurysms Dot haemorrhages	Dot + flame haemorrhages ME, CME, Non-perfusion	—	
	64/M	10	Oral	—	—	20/200	20/30	20/30	20/30	ECCE+IOL	Microaneurysms Dot haemorrhages	Dot + flame haemorrhages ME, CME, Non-perfusion	—	
5	71/M	1	Oral	S/A MI Ischaemic heart disease	—	CF	20/200	CF	20/200	ICCE	NVD?	NVD, vitreous haemorrhage	Post-op. PRP	
	77/M	7	Diet	Chronic lung disease	—	CF		—	20/50	ECCE+IOL	PDR, S/A PRP	PDR, S/A PRP	—	

Op, operation; CF, counting fingers; DR, diabetic retinopathy; ICCE, intracapsular cataract extraction; ECCE, extracapsular cataract extraction; IOL, intraocular lens; A-L, argon laser photocoagulation; ME, macular oedema; CME, cystoid macular oedema; NAG, narrow angle glaucoma; ALI, argon laser iridotomy; NVD, neovascularisation on the disc; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; S/A, state after; MI, myocardial infarction.

closure, retinal ischaemia, and neovascularisation.

Previous authors have pointed out that postoperative progressive changes of diabetic retinopathy occur mainly in patients in whom diabetic retinopathy was already present prior to surgery.^{1-3,6} However, the mechanisms involved in acceleration of diabetic retinopathy after cataract extraction in elderly patients is unknown. Local factors which might account for the sudden vasculopathic deterioration after cataract extraction are: (a) the absence of an angiogenic inhibitory factor which is present in the lens,⁸ (b) postoperative intraocular inflammation mediated by leukotrienes,⁹ (c) reduced secretion of vaso-inhibitory substances present in the retinal pigment epithelium,¹⁰ and (d) increased synthesis of the endothelin that functions as an angiogenic agent within the iris stroma.¹¹ The possible role of each of these factors in the sudden aggravation of diabetic retinopathy after cataract surgery deserves investigation. Whatever the aetiology, the retinal capillaries appear to make a pathological response to the surgery, with resulting disruption of the blood-retinal barrier and/or occlusion of the retinal capillaries. The clinical correlates of these events are transudation and macular oedema and/or induction of retinal ischaemia leading to neovascularisation.

The cases reported here highlight some of the problems of treating diabetic patients with cataract. The first problem relates to the timing of cataract surgery. Since surgery may lead to aggravation of diabetic retinopathy, it may be preferable to delay it as long as possible. On the other hand opacity of the lens can be an obstacle to laser treatment. It can also preclude accurate assessment of the retinopathy, and in particular the amount of retinal ischaemia. Although fluorescein angiography is sometimes helpful in the assessment of retinal ischaemia, even in cases with significant lens opacities, underestimation of the severity of the disease is not uncommon.

Another problem relates to the difficulty of differentiating between aphakic or pseudophakic cystoid macular oedema and diabetic cystoid macular oedema. Indeed, sometimes it is impossible to distinguish between them, since cystoid macular oedema occurs in both conditions. However, as the present series shows, compared with the perifoveal fluorescein leakage seen in non-diabetic aphakic eyes the fluorescein leakage in diabetic eyes is more extensive and extends towards the vascular arcade and peripapillary region. In this series diabetic retinopathy was defined as 'deteriorated' only when ophthalmoscopy disclosed wide areas of retinal thickening and angiography revealed extensive dye leakage from visible microaneurysms in addition to perifoveal leakage from the capillary bed that appears in the general aphakic or pseudophakic cystoid macular oedema. It is not unusual to find a discrepancy between the ophthalmoscopic picture of mild cystoid macular oedema accompanied by good vision and the angiographic appearance of marked fluorescein leakage (cases 3 and 4). Moreover, it is difficult to predict whether the postoperative cystoid macular oedema will resolve spontaneously (as in

cases 3 and 4) or lead to permanent damage. This difficulty may make it hard to decide whether or not to recommend laser treatment.

It has been suggested that extracapsular cataract extraction reduces the risk of postoperative diabetic complications and is therefore preferable to the intracapsular technique.¹²⁻¹⁴ However, in our first patient the postoperative aggravation of diabetic retinopathy was similar in both eyes, even though one eye underwent an intracapsular and the other an extracapsular procedure. Our experience with other operated patients further supports our observation that, although deterioration of diabetic retinopathy is less common after extracapsular than after intracapsular cataract extraction, the extracapsular procedure does not necessarily mean that aggravation of pre-existing diabetic retinopathy can be prevented.

The question whether or not to perform preventive preoperative laser photocoagulation in patients with diabetic retinopathy is also of some concern. In our fifth patient, aggravation of retinal neovascularisation in the first operated eye was evident within a month after surgery. In the fellow non-operated eye retinal neovascularisation showed significant progression only three years later; prior to cataract extraction in that eye, panretinal laser photocoagulation was applied and the new blood vessels then regressed. The diabetic retinopathy in that eye did not progress after surgery. This raises an important question: should those patients with cataracts but with adequate fundus visualisation receive preventive laser treatment even when the preoperative severity of diabetic retinopathy does not meet the criteria for laser treatment outlined by the Diabetic Retinopathy Multi-center Studies? The answer to this question must await the findings of suitably controlled studies.

Our findings emphasise the need for a careful assessment of the diabetic retinopathy prior to surgery. This should include fluorescein angiography, which can be helpful even when visualisation of the fundus is impaired. After surgery follow-up examinations to detect any aggravation of diabetic retinopathy should be performed at weekly or two-weekly intervals for the first three months and every four weeks for the next three months. Fluorescein angiography should be performed during the first month of follow-up, as well as three and six months after surgery, even in the absence of clinical signs of deterioration of diabetic retinopathy. Since it is more sensitive than ophthalmoscopy as a diagnostic tool, it should also be performed whenever such deterioration is suspected. If aggravation of diabetic retinopathy following cataract surgery is detected early and treated with laser photocoagulation, the final visual outcome may be improved.

- 1 Kirmani TH. Prognosis of cataract extraction in diabetics. *Am J Ophthalmol* 1964; 57: 617-9.
- 2 Caird FI, Hutchinson M, Pirie A. Cataract extraction and diabetes. *Br J Ophthalmol* 1965; 49: 466-71.
- 3 Clayman HM, Jaffe NS, Light DS. Lens implantation and diabetes mellitus. *Am J Ophthalmol* 1979; 88: 990-2.
- 4 Kennedy JE, Lim ASM, Ang BC. Posterior chamber intraocular lenses in diabetics. *Aust NZ J Ophthalmol* 1984; 12: 253-6.
- 5 Straatsma BR, Petit TH, Wheeler N, Miyamasu W. Diabetes mellitus and intraocular lens implantation. *Ophthalmology* 1983; 90: 336-43.

- 6 Apple DJ, Mamalis N, Loftfield K, *et al.* Complications of intraocular lenses. A historical and histopathological review. *Surv Ophthalmol* 1985; 29: 1-54.
- 7 Jaffe GJ, Burton TC. Progression of nonproliferative diabetic retinopathy following cataract extraction. *Arch Ophthalmol* 1988; 106: 745-9.
- 8 Williams GA, Eisenstein R, Schumacher B, Hsiao KC, Grant D. Inhibition of vascular endothelial cell growth in the lens. *Am J Ophthalmol* 1984; 97: 366-71.
- 9 Milch FA, Yannuzzi LA. Medical and surgical treatment of aphakic cystoid macular edema. *Int Ophthalmol Clin* 1987; 27: 205-17.
- 10 Glaser BM, Campochiaro PA, David JL Jr. Retinal pigment epithelial cells release an inhibitor of neovascularization. *Arch Ophthalmol* 1985; 103: 1870-5.
- 11 MacCumber M, Ross C, Delayre T, Synder S, Glaser BM. Ocular synthesis of and response to endothelin, a potent vasoconstrictive peptide. Second International Symposium on Ocular Circulation and Neovascularization. Abstract, 1989: 33.
- 12 Alpar JJ. Cataract extraction and diabetic retinopathy. *J Am Intraocul Implant Soc* 1984; 10: 433-7.
- 13 Alpar JJ. Diabetes, cataract extraction and intraocular lenses. *J Cataract Refract Surg* 1987; 13: 43-6.
- 14 Poliner LS, Christianson DJ, Escoffery RF, Kolker AE, Gordon ME. Neovascular glaucoma after intracapsular and extracapsular cataract extraction in diabetic patients. *Am J Ophthalmol* 1985; 100: 637-43.

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USES

Glauline is a beta adrenoceptor blocking agent used in the topical treatment of chronic open-angle glaucoma and other conditions in which intra-ocular pressure is elevated above normal levels.

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Adults and the elderly: The recommended dosage is one drop instilled into the affected eye(s) twice daily.

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Newly diagnosed patients with ocular hypertension or chronic open-angle glaucoma should be treated with Glauline 0.1%, changing to the higher strength if adequate control of intra-ocular pressure is not achieved. Patients on existing therapy, whether or not this is to be continued, should receive Glauline 0.3%.

CONTRAINDICATIONS, WARNINGS, ETC

Contraindications: Bronchial asthma, history of bronchial asthma, chronic obstructive airways disease, sinus bradycardia, second or third degree atrio-ventricular block, cardiac failure, cardiogenic shock, hypersensitivity to any of the components of the preparation.

Precautions and Warnings: As with other topically applied beta-blockers, systemic absorption may occur causing adverse reactions similar to those of orally administered beta-blockers. Cardiac and respiratory reactions have been reported with topically applied beta-blockers including, rarely, death due to bronchospasm or cardiac failure. Congestive cardiac failure should be adequately controlled before starting therapy with Glauline. If the patient has a history of cardiac disease, pulse rate should be monitored. Metabolic control should be monitored during Glauline therapy in patients with labile diabetes. There have been reports of granulomatous anterior uveitis occurring in patients using Glauline. In any case, where a patient shows symptoms or signs suggestive of anterior uveitis, Glauline should be withdrawn and an alternative ocular antihypertensive agent substituted. Glauline contains benzalkonium chloride as a preservative and should therefore not be used in patients continuing to wear soft (hydrophilic) contact lenses. Use in pregnancy: Although there is no evidence to suggest that metipranolol has teratogenic properties, its use during pregnancy should be avoided unless the potential benefits are considered to outweigh the possible hazards.

Use in lactation: As beta-blockers can pass into breast milk, consideration should be given to stopping breast-feeding if therapy with Glauline is considered necessary.

Side-effects:

Ocular: Transient burning or stinging on instillation, blurred vision, superficial punctate keratitis, pharyngoconjunctivitis and anterior uveitis have been reported.

Cardiovascular: Bradycardia and hypotension can occasionally occur following the systemic absorption of locally applied beta-blockers.

Respiratory: Bronchospasm can occur, predominantly in patients with a history of reversible obstructive airways disease. Dyspnoea and respiratory distress have also been reported with topically applied beta-blockers.

CNS: Headache, ataxia, weakness and lethargy can occur.

Dermatological: Local manifestations of contact sensitivity reactions around the eyes can involve skin rashes on the lower lids and cheeks, and peri-orbital oedema.

Interactions: Caution should be exercised if used in conjunction with oral beta-blockers as additive effects on systemic beta blockade may occur. Overdosage: Overdosage is unlikely by the ocular route. If excess is accidentally administered to the eye, the affected eye should be immediately flushed with water or saline. If accidental or deliberate systemic ingestion has taken place, bronchospasm, bradycardia, hypotension and cardiac failure may result, and treatment for overdose of a beta-receptor blocking agent should be instituted.

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Glauline should not be diluted or dispensed from any container other than the original bottle. The unopened product has a shelf life of 3 years, but as with other eye drops the contents of each bottle should be discarded one month after opening.

LEGAL CATEGORY POM

PACKAGE QUANTITIES

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OTHER INFORMATION

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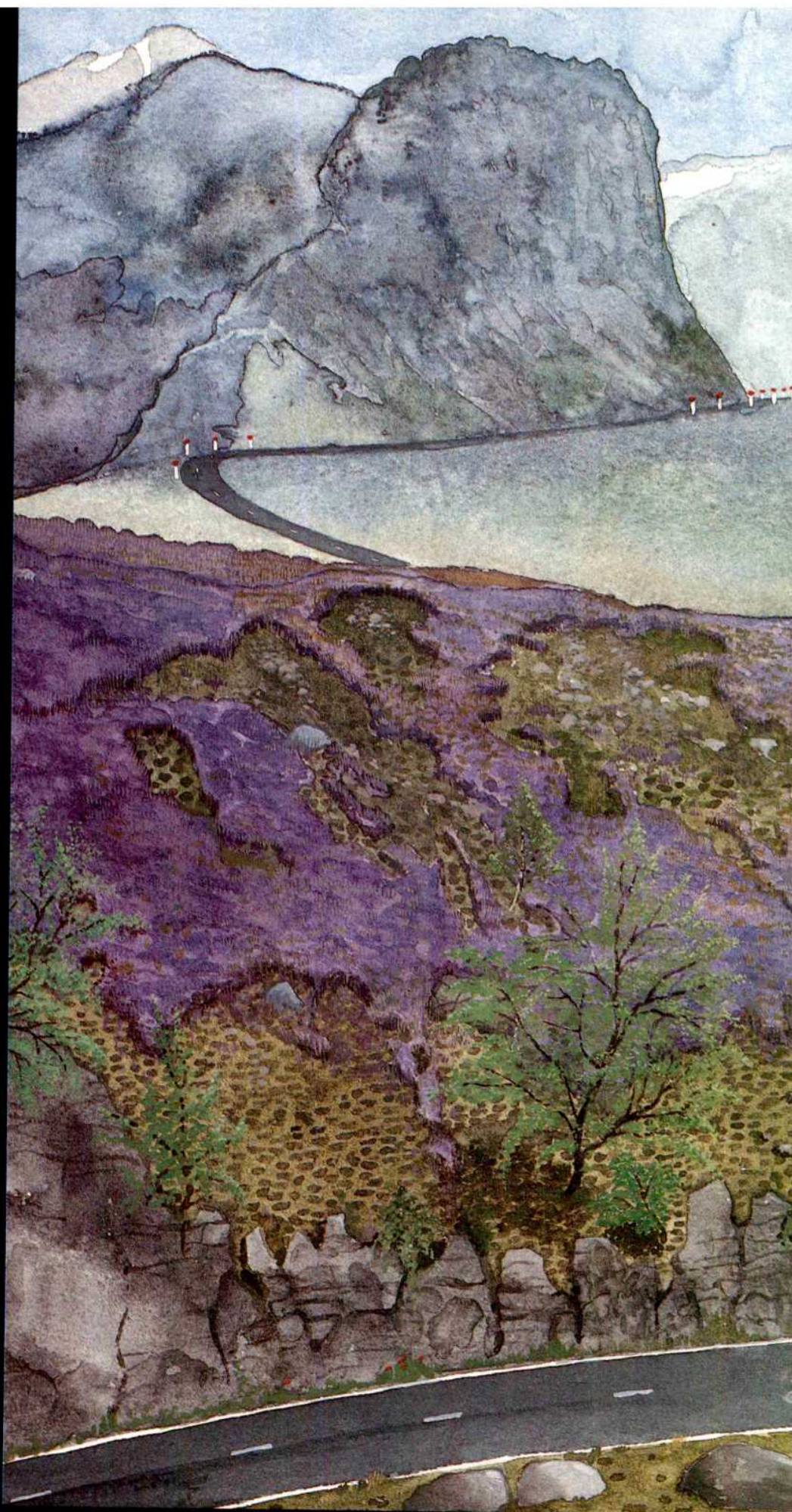
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Comparison between Heparin
surface modified IOLs and
normal IOLs in the same patient.



This female has a history of
longstanding diabetes and
glaucoma.

A. Slit lamp

B. Specular microscopy

Right eye — NORMAL
PMMA LENS

- 11 months post-operatively
- Confluent giant cells can be
seen clearly on both slides



C. Slit lamp

D. Specular microscopy

Left eye — HEPARIN
SURFACE MODIFIED LENS

- 6 months post-operatively
- No giant cells
- Newton's rings seen clearly

A clear case
for Heparin
surface modified
IOLs.

Extracapsular cataract surgery with lens implantation in diabetics with and without proliferative retinopathy

I A Cunliffe, D W Flanagan, N D L George, R J Aggarwal, A T Moore

Abstract

In a retrospective study we have examined all diabetics (66 operated eyes) and an equal number of non-diabetic matched controls who underwent extracapsular cataract extraction (ECCE) with intraocular lens (IOL) implantation over a two-year period ending in December 1987. Of the diabetic patients' 76% eyes improved by at least two lines of Snellen acuity postoperatively. Of these patients 68% eyes and of the control eyes 83% achieved an acuity of 6/12 or better. In the diabetics the visual outcome depended on the state of the retinopathy and in particular the maculopathy. The diabetic group had a greater incidence of postoperative inflammation, but the major complications were related to continuing neovascularisation. Early postoperative laser photocoagulation may help to prevent these proliferative complications, and, provided a large, adequate capsulotomy is performed for capsular thickening, the presence of an IOL does not interfere with this photocoagulation. We also advise early postoperative assessment, and treatment if necessary, of any maculopathy. Diabetic retinopathy should no longer be regarded as a contraindication to intraocular lens insertion.

Diabetes mellitus is a common condition, affecting 1-2% of the population. Cataract occurs earlier in diabetics than in non-diabetics, and both cataract and retinopathy are related to the age of the patient and the duration of the diabetes.^{1,2} Cataract surgery in diabetics may be performed to improve vision or to allow assessment and treatment of retinopathy. The benefits of intraocular lenses (IOLs) over other forms of aphakic correction are well known, and most surgeons now perform extracapsular cataract extraction (ECCE) with IOL implantation for senile cataract. Currently in the United Kingdom over 90% of cataract extractions include implantation of an IOL.³ IOL implantation in diabetics, especially in those with proliferative retinopathy, is still controversial³⁻⁷ and is still listed by some manufacturers as a contraindication to their use. We now routinely implant lenses in all diabetics, and this study reviews our results.

Patients and methods

We have reviewed 66 consecutive diabetic patients (72 operated eyes) undergoing ECCE plus IOL under the care of two consultant ophthalmologists over a two-year period ending

in December 1987. The minimum follow-up was 18 months. Six patients were excluded from the study: four who died within 18 months of surgery, one myopic patient (no IOL), and one patient lost to follow-up. Six patients have had both eyes operated on. Sixty-six eyes were included in the study, of which 63 have been re-examined by one of the authors. Each diabetic eye was matched for age and surgeon with a non-diabetic eye undergoing ECCE+IOL; this formed the control group, who were also recalled for examination. Three of the diabetics and two of the controls who have died, but who had completed more than 18 months' follow-up, are included.

All patients received preoperative mydriatic drops, and patients under the care of one of the consultants received preoperative indomethacin (0.5%) drops to help prevent surgically induced miosis. The surgical procedure was a standard corneal section ECCE with posterior chamber two-piece J-loop IOL, with the following exceptions: two eyes in each group had limbal sections; one eye in each group had an anterior chamber IOL; two eyes of diabetic patients had one-piece (all polymethyl methacrylate) IOLs.

There was no statistically significant difference between the control group and the diabetic group when compared for age (t test $p>0.1$), sex, anaesthetic, or use of sodium hyaluronate (Healon id) or indomethacin (χ^2 , $p>0.5$). There were 28 males and 38 females in each group, and their ages ranged from 22 to 91 years (mean 70.5) in the diabetic group and from 46 to 88 years (mean 73.9) in the control group. The mean follow-up time was 2.61 years. In each group 44 eyes (66.7%) were operated on by one of two consultants, and 22 eyes (33.3%) by one of seven junior staff.

In the diabetic group 11 patients (16.7%) were controlled by diet, 39 (59.1%) were controlled on oral hypoglycaemic agents alone, 15 (22.7%) were on insulin, and one (1.5%) required both

Table 1 Coexistent diseases in the diabetic and control groups

Coexistent disease	Diabetics	Controls
ARMD	5	2
COAG	5	6
Endothelial guttata	2	3
Branch vein occlusion	1	1
Iritis	0	1
Amblyopia	1	0
Lamellar hole	0	1
Interstitial keratitis	1	0
Amiodarone keratopathy	0	1
Ocular hypertension	0	1
Pituitary adenoma	0	1

ARMD=age related macular degeneration.
COAG=chronic open angle glaucoma.

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Table 2 Final visual outcome

	Final visual acuity: number of eyes (%)				Total
	≥6/12	6/18-6/24	6/36-6/60	<6/60	
Controls	55 (83.3)	7 (10.6)	3 (4.5)	1 (1.5)	66
Diabetics	45 (68.1)	6 (9.1)	7 (10.1)	8 (12.2)	66
No retinopathy	28 (84.8)	4 (12.1)	0 (0)	1 (3.0)	33
Background					
+Maculopathy	3	0	4	4	
-Maculopathy	10 (56.5)	1 (4.3)	1 (21.7)	0 (17.4)	23
Proliferative					
+Maculopathy	2	1	2	3	
-Maculopathy	2 (40)	0 (10)	0 (20)	0 (30)	10

+ = With. - = Without.

Table 3 Diagnosis in eyes failing to achieve postoperative acuity of 6/12 or better

	Controls	Diabetic retinopathy		
		Nil	Background	Proliferative
ARMD	7	2	0	0
Diabetic maculopathy	0	1	9	6
Macular vein occlusion	1	0	0	0
Myopic maculopathy	1	0	0	0
Retinal detachment	1	0	0	0
Corneal oedema	0	0	1	0
Amblyopia	0	1	0	0
Endophthalmitis	0	1	0	0
Lamellar hole	1	0	0	0

ARMD=age related macular degeneration.

insulin and oral medication. The duration of diabetes in the oral hypoglycaemic group ranged from 1 to 42 years (mean 12.3) and in the insulin dependent group from 2 to 49 years (mean 22.4). Thirty-three patients (50%) had no retinopathy, 23 (34.8%) had background retinopathy (11 with maculopathy), and 10 (15.2%) had proliferative retinopathy (8 with maculopathy). Several coexistent diseases were present preoperatively (Table 1).

Results

VISUAL RESULTS

There was no statistically significant difference in visual outcome (defined as ≥6/12 vision) between controls and diabetics without retinopathy (χ^2 , $p>0.5$). Diabetics with retinopathy had a significantly poorer outcome when compared with controls (χ^2 , $p<0.01$). The visual results were poorest in those with diabetic

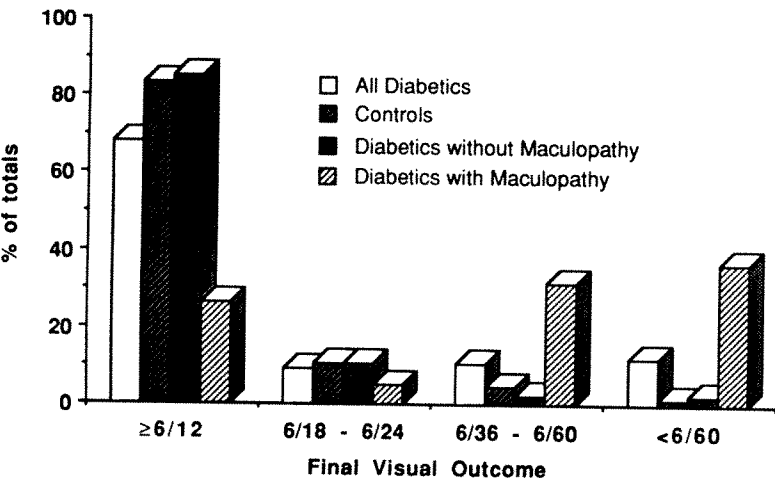


Figure 1 Histogram showing the final visual outcome of diabetic eyes with and without maculopathy and controls.

maculopathy or proliferative retinopathy (Table 2, Figs 1, 2). The main causes for an acuity of <6/12 were age related macular degeneration and diabetic maculopathy (Table 3).

In eyes with proliferative retinopathy or maculopathy it may be more useful to consider improvement in vision rather than final visual acuity. In the proliferative group six of 10 eyes showed an improvement of ≥2 lines Snellen acuity, and in those with maculopathy seven of 19 showed an improvement of ≥2 lines Snellen acuity (Fig 3).

PROGRESSION OF RETINOPATHY

Twenty-five diabetics showed progression of retinopathy in the follow-up period. Five eyes without retinopathy preoperatively developed background retinopathy (one with maculopathy). In the background group two eyes developed a new maculopathy, four eyes showed progression of pre-existing maculopathy, and six eyes developed preproliferative or proliferative retinopathy. In these last six eyes the maculopathy also progressed (in four within six months of surgery), while the fellow eye remained stable. In the proliferative group five eyes developed further new vessels and six showed progression of their maculopathy (three within six months of surgery). Overall, nine eyes developed severe maculopathy in the early postoperative period. Seven of these had pre-existing maculopathy and five had had previous laser photocoagulation.

Seventeen eyes required laser treatment postoperatively. Three eyes had panretinal photocoagulation (PRP) only, seven eyes had focal macular treatment only, and seven eyes had combined PRP and focal macular treatment. In none of these cases did the presence of an IOL prevent adequate photocoagulation.

COMPLICATIONS

There were few operative complications. In the control group, there was one case of vitreous loss and one posterior capsule tear. There were no operative complications in the diabetic group.

Of the postoperative complications macular oedema (diabetic and cystoid), severe inflammation, rubeosis iridis, neovascular glaucoma, and vitreous haemorrhage occurred more frequently in the diabetic group (Table 4). Four diabetics' eyes and five control eyes developed classical cystoid macular oedema postoperatively; all

Table 4 Postoperative complications

Postoperative complications	Diabetics	Controls
Rubeosis and neovascular glaucoma	4	0
Macular oedema (diabetic and cystoid)	17	5
Severe inflammation		
Iritis	4	2
Sterile hypopyon	1	1
Fungal keratitis	1	0
Endophthalmitis	1	0
Suture infiltrate	1	0
Vitreous haemorrhage	4	0
Synechiae to IOL	9	6
Capsular thickening	23	17
IOL malposition	2	0
Iris prolapse	1	2
Retinal detachment	0	1
Corneal decompensation	1	0

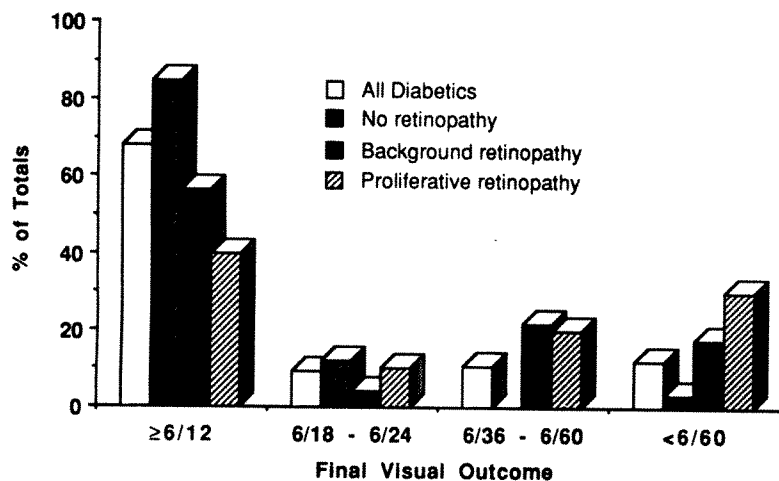


Figure 2 Histogram of the final visual outcome of diabetic eyes with and without retinopathy.

resolved completely. Thirteen diabetics developed diabetic macular oedema in the follow-up period. Seven diabetics' eyes showed evidence of continuing neovascularisation; three developed vitreous haemorrhage and four developed rubeosis iridis. Three of the latter group progressed to neovascular glaucoma. In addition one diabetic patient's eye had a vitreous haemorrhage due to posterior vitreous detachment. The three eyes that developed neovascular glaucoma achieved a final vision of <6/60. In the fourth case the rubeosis regressed after PRP with the retention of 6/12 vision and a normal intraocular pressure.

Severe inflammation or infection, defined as iritis persisting for more than six weeks postoperatively, endophthalmitis, or keratitis, was more common in the diabetic group (Table 4).

Discussion

In the past diabetic retinopathy has been considered a contraindication to IOL implantation, though many surgeons now routinely implant IOLs in diabetics. Although there have been several reports of the results of cataract extraction with implants in diabetics,^{2-8,17} many have included few cases of proliferative retinopathy and have short periods of follow-up.

In this study diabetics without retinopathy achieved visual results comparable to those of controls. The patients with diabetic retinopathy,

particularly with maculopathy, fared less well. However, patients with maculopathy or severe retinopathy may have valuable visual improvement after surgery, and a clear optical axis may allow adequate laser photocoagulation to stabilise vision. Six of 10 eyes with proliferative retinopathy and seven of 19 eyes with pre-existing maculopathy maintained ≥ 2 lines improvement in Snellen acuity at a mean of 2.76 years follow-up (Figs 1-3). At final follow-up a total of 15 eyes had proliferative retinopathy and nine have maintained an improvement of ≥ 2 lines Snellen acuity. Patients with proliferative retinopathy may achieve a worthwhile visual improvement so long as adequate preoperative (where possible) or early postoperative laser treatment is performed. We encountered no difficulty in performing laser photocoagulation through the IOL, and we consider that this group of patients should not be excluded from the optical advantages of an IOL.

In diabetics with pre-existing retinopathy cataract surgery has been reported to cause a severe form of exudative maculopathy in the early postoperative period.¹⁸ This occurred in nine eyes in our study. Seven of these eyes had pre-existing maculopathy and five had had previous laser treatment. Although the progression of maculopathy occurred soon after surgery, it is difficult to know whether the surgery was incidental. Several contributory mechanisms – for example, intraocular inflammatory mediators such as prostaglandins¹⁹ – may be involved, but the aetiology remains obscure. But it is important that early postoperative assessment and treatment where necessary are performed.²⁰

Patients with proliferative retinopathy who undergo lens extraction are at risk of developing rubeosis iridis, neovascular glaucoma, and vitreous haemorrhage.^{21,22} Poliner *et al* suggested that an intact capsule helps to prevent the development of rubeosis.²² In our study four eyes each with pre-existing proliferative retinopathy developed rubeosis at 12 to 18 months after surgery. Two of these occurred at four and five months respectively following YAG laser capsulotomy. It is clear that eyes with and without an intact capsule may develop rubeosis iridis, and early panretinal photocoagulation is needed to prevent development of rubeotic glaucoma.²³

Previous reports⁴⁻⁷ have considered that an IOL and capsular thickening may prevent adequate postoperative laser treatment. In our study 23 diabetic eyes had distinct capsular thickening and 17 eyes received postoperative laser treatment (10 with PRP). Early, large capsulotomies can overcome the problems created by capsular thickening, and we encountered no difficulties in performing this laser treatment.

In conclusion, we consider that diabetics should no longer be excluded from the optical advantages of an IOL and that they have satisfactory visual results from this form of aphakic correction. However, these patients should be followed up closely postoperatively and any progressive retinopathy treated promptly.

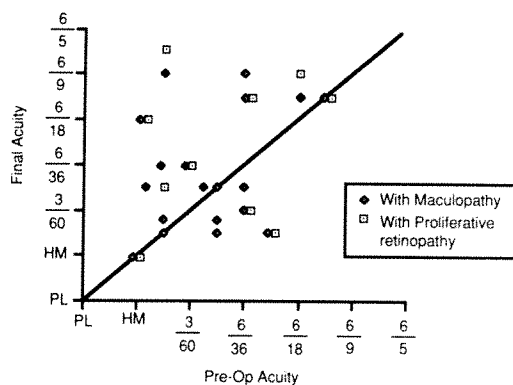


Figure 3 Scatter plot of preoperative and final visual acuity of diabetic eyes with proliferative retinopathy and maculopathy. Touching symbols are the same patient.

1 Klein BEK, Klein R, Moss SE. Prevalence of cataracts in a population-based study of persons with diabetes mellitus. *Ophthalmology* 1985; 92: 1191-6.

- 2 Straatsma BR, Pettit TH, Wheeler N, Miyamasu W. Diabetes mellitus and intraocular lens implantation. *Ophthalmology* 1983; 90: 336-43.
- 3 Beckett R, Rosen ES. Results of the 1988 Survey on Cataract Surgery and Intraocular Lens Implantation in the United Kingdom. *Eur J Implant Refract Surg* 1989; 1: 231-5.
- 4 Thompson SM, Kritzinger EE, Roper-Hall MJ. Should diabetes be a contraindication for an intraocular lens? *Trans Ophthalmol Soc UK* 1983; 103: 115-7.
- 5 Patz A. Photocoagulation of retinal, vascular, and macular diseases through intraocular lenses. *Ophthalmology* 1981; 88: 398-406.
- 6 Jaffe NS. The way things were and are: changing indications for intraocular lens implantation. *Ophthalmology* 1983; 90: 318-20.
- 7 Tasman W. Are there any retinal contraindications to cataract extraction and posterior chamber lens implants? *Arch Ophthalmol* 1986; 104: 1767-8.
- 8 Clayman HH, Jaffe NS, Light DS. Lens implantation and diabetes mellitus. *Am J Ophthalmol* 1979; 88: 990-2.
- 9 Sebestyen JG, Wafai MZ. Experience with intraocular lens implants in patients with diabetes. *Am J Ophthalmol* 1983; 96: 94-6.
- 10 Kennedy JE, Lim ASM, Ang BC. Posterior chamber intraocular lenses in diabetics. *Aust J Ophthalmol* 1984; 12: 253-6.
- 11 Alpar JJ. Cataract extraction and diabetic retinopathy. *J Am Intraocul Implant Soc* 1984; 10: 433-7.
- 12 Ngui MSH, Lim ASM, Chong AB. Posterior chamber intraocular lenses in diabetics. *Int Ophthalmol* 1985; 8: 257-9.
- 13 Sebestyen JG. Intraocular lenses and diabetes mellitus. *Am J Ophthalmol* 1986; 101: 425-8.
- 14 Alpar JJ. Diabetes: Cataract extraction and intraocular lenses. *J Cataract Refract Surg* 1987; 13: 43-6.
- 15 Fung WE. Phacoemulsification and implantation of posterior chamber intraocular lenses in eyes with quiescent proliferative diabetic retinopathy. *Graefes Arch Clin Exp Ophthalmol* 1987; 25: 251-3.
- 16 Hutton WL, Pesicka GA, Fuller DG. Cataract extraction in the diabetic eye after vitrectomy. *Am J Ophthalmol* 1987; 104: 1-4.
- 17 Cheng H, Franklin SL. Treatment of cataract in diabetics with and without retinopathy. *Eye* 1988; 2: 607-14.
- 18 Jaffe GJ, Burton TC. Progression of nonproliferative diabetic retinopathy following cataract extraction. *Arch Ophthalmol* 1988; 106: 745-9.
- 19 Milch FA, Yannuzzi LA. Medical and surgical treatment of aphakic cystoid macular oedema. *Int Ophthalmol Clin* 1987; 27: 205-17.
- 20 Early Treatment Of Diabetic Retinopathy Study Research Group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular oedema. Early Treatment Of Diabetic Retinopathy Study Report No. 2. *Ophthalmology* 1987; 94: 761-74.
- 21 Aiello LM, Wand M, Liang G. Neovascular glaucoma and vitreous hemorrhage following cataract surgery in patients with diabetes mellitus. *Ophthalmology* 1983; 90: 814-9.
- 22 Poliner LS, Christianson DJ, Escoffery RF, Kolker AE, Gordon ME. Neovascular glaucoma after intracapsular and extracapsular cataract extraction in diabetic patients. *Am J Ophthalmol* 1985; 100: 637-43.
- 23 Murphy RP, Egbert PR. Regression of iris neovascularisation following panretinal photocoagulation. *Arch Ophthalmol* 1979; 97: 700-2.

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- REFERENCES:** 1. Jones FJ, Ekberg NJ, Letter N Engl J Med 1979; **301**: 270.
2. Levy NS, Boone L, Ellis E. Glaucoma 1985; **7**: 54-62.
3. Schoene RB, Abuan T, Ward RL, Brasley CH. Am J Ophthalmol 1984; **97**: 86-92.
4. Van Buskirk EM. New Trends in Ophthalmol 1986; **104**: 1178-1184.

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Cotton-wool spots and retinal light sensitivity in diabetic retinopathy

Toke Bek, Henrik Lund-Andersen

Abstract

In 14 eyes of 14 patients with diabetic retinopathy the light sensitivity of retinal cotton-wool spots was studied by computerised perimetry, and the visual field data were accurately correlated with the corresponding morphology as seen on fundus photographs and fluorescein angiograms. In 12 of the eyes the examinations were repeated within one year in order to follow changes in retinal light sensitivity during the evolution of the lesions. Retinal cotton-wool spots were in all eyes associated with localised non-arcuate scotomata in the visual field. In four eyes the cotton-wool spots disappeared within three months of the first examination, and in two of these cases the corresponding scotomata disappeared together with the morphological lesions. In eight eyes the cotton-wool spots (and the corresponding scotomata) had not resolved one year after the first examination. The mean blood pressure showed no significant difference between the patients in whom the lesions resolved within three months and the patients in whom the lesions persisted longer.

The retinal cotton-wool spot is a frequent finding in a variety of diseases which involve the ocular fundus.¹ In diabetic retinopathy the lesion may be among the initial signs of the disease, and when the lesions are numerous they may indicate

rapidly progressing retinopathy.² Although it is known that the cotton-wool spot can be caused by focal retinal ischaemia, no single explanation has been given which consistently accounts for the aetiology of the lesion in all cases.³

The retinal cotton-wool spot has been mainly investigated by photographic and histological techniques which demonstrate the morphological aspects of the lesion. The inclusion of techniques for the assessment of neurosensory function can be expected to supplement our understanding of its pathophysiology. In a prior study the visual field of six diabetic patients with retinal cotton-wool spots was examined by a manual perimetric technique,⁴ but the exact correlation between visual field data and the corresponding fundus morphology was not accounted for, and the visual field findings were not systematically followed during the evolution of the lesions.

In the present study the light sensitivity of retinal areas with cotton-wool spots was examined by computerised perimetry, and by a newly developed optical technique the visual field data were accurately correlated with the corresponding fundus morphology as seen on fundus photographs and fluorescein angiograms. The examinations were repeated within one year in order to follow changes in retinal light sensitivity during the evolution of the lesions.

Materials and methods

SUBJECTS

Fourteen eyes of 14 patients with insulin dependent diabetes mellitus in which retinal cotton-wool spots had been detected by fundoscopic examination were subjected to computerised perimetry, and the visual field data were accurately correlated with the corresponding morphology as seen on fundus photographs and fluorescein angiograms. The patients underwent routine ophthalmic examinations, including visual acuity, slit-lamp examination, tonometry, ophthalmoscopy, fundus photography, and fluorescein angiography. Their informed consent was obtained. The blood pressure was measured at the initial examination or was obtained from medical records within two months of the initial examination. The ametropia of the eyes ranged between -2.0 D and $+1.25$ D, and the most severe astigmatism was 1.5 DC. Visual acuity was $6/9$ in one patient and $6/6$ or better in all the other patients.

Except for fundoscopic signs of retinopathy the other part of the ophthalmological examination was normal in all the patients included. In 12 eyes the examinations were repeated within three months of the first examination and, in cases

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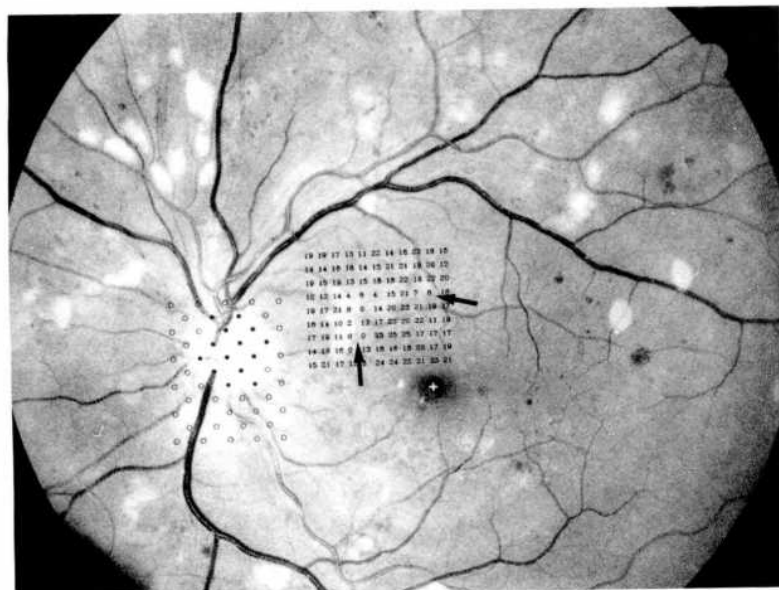


Figure 1A A left eye fundus photograph of a patient with diabetic retinopathy dominated by cotton-wool spots. The perimetric stimulus pattern extended from degree co-ordinates $(x, y) = (-9, -10)$ to $(1, -2)$, and the visual field data have been superimposed on to the corresponding fundus morphology. Two areas with low decibel values are seen to correlate with retinal cotton-wool spots (arrows). The low decibel values are predominantly located on the peripheral aspect of the lesions.

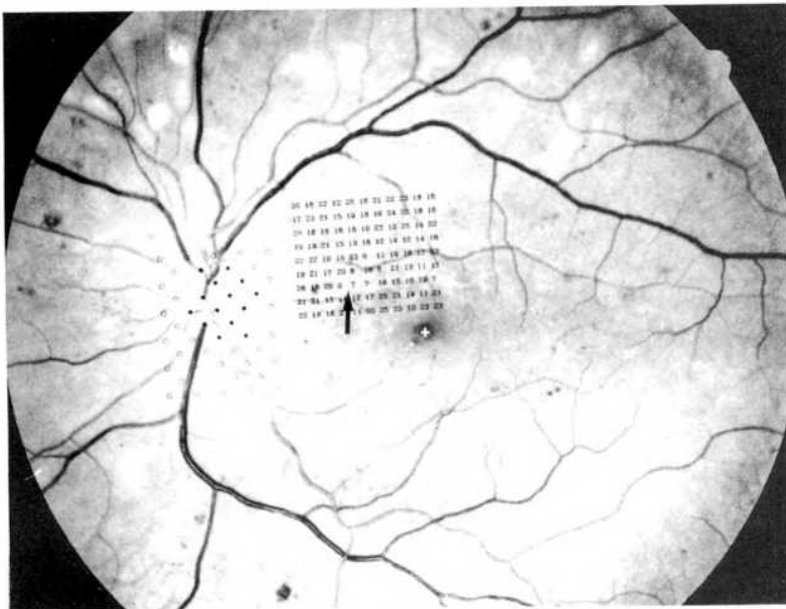


Figure 1B A fundus photograph of the same eye three months later. The cotton-wool spots which were studied by perimetry have now resolved, but an area with low decibel values persists where one of the cotton-wool spots was located (arrow). Another cotton-wool spot has now appeared below the examined area.

where the cotton-wool spots persisted, again one year after the initial examination.

PHOTOGRAPHY

Photography was performed with a Canon CF-60Z fundus camera employing Ektachrome 64 (EPR 135-36) film for fundus photography, and Ilford HP-5 black-and-white film for fluorescein angiography. 5 ml 10% fluorescein sodium was injected into an antecubital vein for fluorescein angiography. Angiograms were taken of the central fundus in fast sequence during the filling phase of the vessels, and at regular intervals until 15 min after injection. Prior to photography cycloplegia and mydriasis were induced with metaxedrine 10% and tropicamide 1% eyedrops.

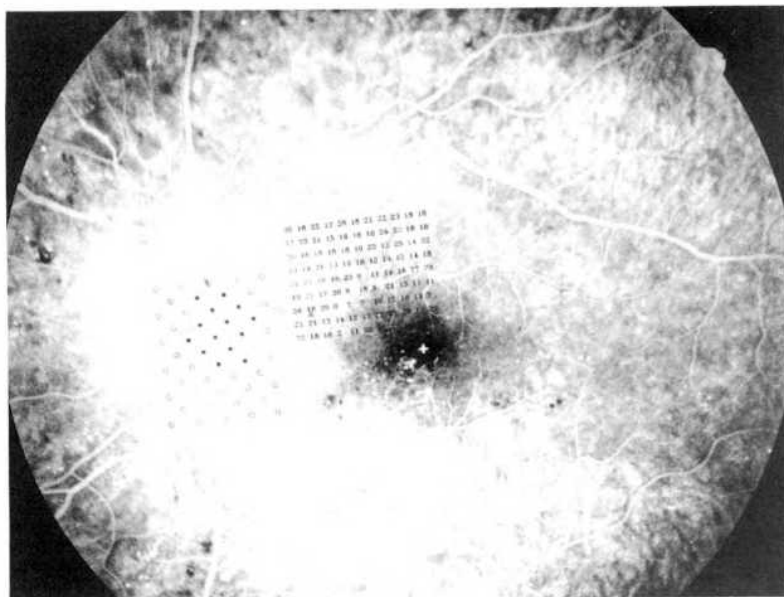


Figure 1C A fluorescein angiogram of the same eye obtained on the same day as Fig 1B, and visual field data have been superimposed. The retinal areas corresponding to the persisting scotoma shows some pathology, mainly as focal leakage of fluorescein.

PERIMETRY

Perimetry was carried out with a Humphrey Field Analyzer (HFA). Full-threshold examinations were performed in stimulus patterns with a density of 1° employing Goldmann stimulus size I. These were the best parameters available on the HFA for the detection of small scotomata. Since the minimum density of customised stimulus patterns on the HFA is 2°, four intersecting patterns with a displacement of 1° in the vertical and the horizontal plane were subsequently tested, and finally merged. The stimulus patterns were placed in areas of the visual field that approximately corresponded to the retinal areas where morphological lesions had been observed by prior fundoscopic examination.

Threshold values that deviated more than 5 dB from the expected value calculated on the basis of answers from adjoining points were retested (standard procedure on the HFA). The blind spot was delimited with Goldmann stimulus size II with a single intensity of 10 dB in two special point patterns located in the area of the blind spot, one (pattern A) extending from degree co-ordinates (x,y)=(11,-7) to (19,3) and one (pattern B) from degree co-ordinates (x,y)=(12,-8) to (18,2). By merging these two patterns a spatial resolution of 1.4° could be obtained in this area. All patients could see the perimeter screen sharply during perimetry without the addition of a corrective lens. Fixation was continuously checked on the fixation monitor supplied on the HFA, which displays the eye on a video screen during perimetry. Fixation was stable during all test sessions in all the patients included.

SUPERIMPOSITION TECHNIQUE

The superimposition of visual field data on to fundus pictures was carried out according to a technique previously described.⁶ This technique is applicable to a fundus photograph (subtending approximately 60° with the camera employed here) with the foveal region in the centre and with the accuracy of the overlay or visual field data on to the corresponding fundus photograph more than 1°. Briefly, with knowledge of the optical imaging in the fundus camera, the visual field printout is reduced to match the size of the corresponding fundus photograph. The visual field is inverted about a horizontal axis, and the overlay is subsequently done on the basis of two points of reference. One of them, the fixation point in the visual field, is laid over the foveola on the fundus picture, and the other, the blind spot in the visual field, is laid over the optic nerve head on the fundus picture.

Results

In Figs 1 to 3 representative examples of visual field data correlated with corresponding fundus morphology are shown. The numbers indicate threshold decibel values obtained with Goldmann stimulus size I, and each number has been superimposed on to the corresponding fundus morphology. In points where the threshold has been tested twice, the average of the two decibel values has been employed. The fixation point is

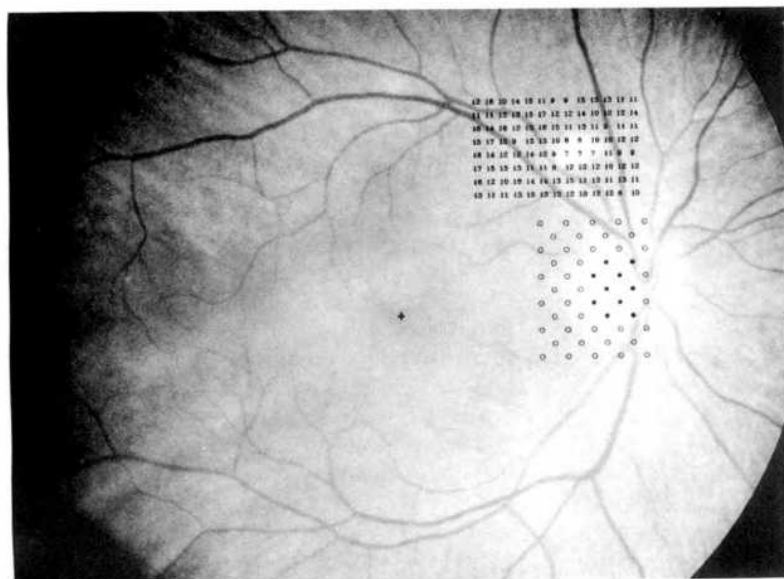


Figure 2A A right eye fundus photograph of a patient with insulin dependent diabetes mellitus. The only sign of retinopathy is a cotton-wool spot located above the optic nerve head. The perimetric stimulus pattern extended from degree co-ordinates $(x, y) = (6, -16)$ to $(18, -9)$. The visual field data have been superimposed on to the corresponding fundus morphology, and low decibel values (a relative scotoma) have been superimposed on to the cotton-wool spot.

indicated with a cross. In the screening tests employed to delimit the blind spot open circles indicate seen points, whereas closed circles indicate points not seen.

In all 14 eyes examined the retinal cotton-wool spots were associated with localised scotomata in the visual field which appeared non-arcuate within the area of the visual field tested. In five of these cases the non-functioning retinal area corresponding to the scotoma extended beyond the peripheral aspect of the morphological lesion (see Fig 1), a finding which could not be explained as a result of inaccuracies of the superimposition technique.

Twelve eyes were re-examined. In four eyes the lesion had disappeared within three months

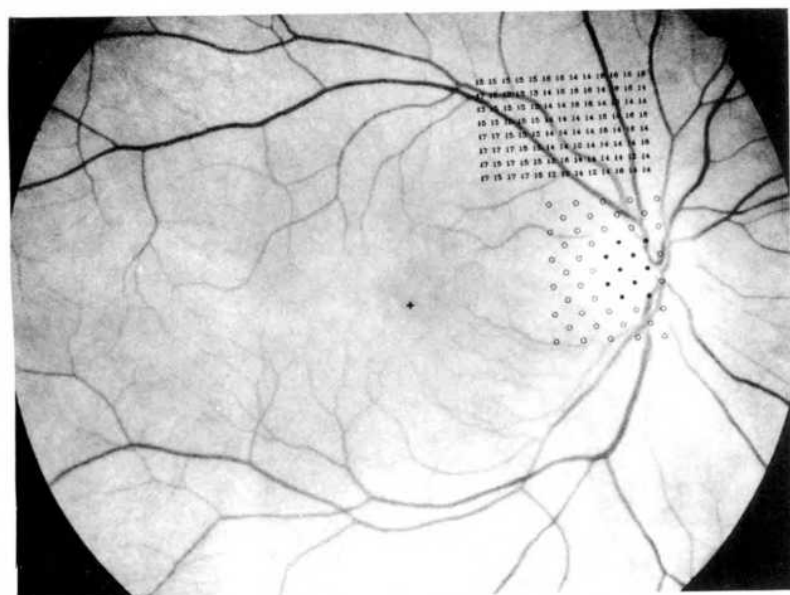


Figure 2B A fundus photograph of the same eye three months later. Visual field data obtained at that time are superimposed. The cotton-wool spot has now entirely disappeared, and no scotoma is detected in the visual field.

of the initial examination. In two of these cases the scotoma and some angiographical pathology corresponding to the now resolved cotton-wool spot persisted (Fig 1). In the other two cases the scotoma had disappeared together with the fundus lesion, and no angiographic traces of the lesion persisted (Fig 2). In eight eyes the cotton-wool spots, though changed in appearance, were still present together with the corresponding visual field scotomata one year from the initial examination (Fig 3).

There was no significant difference between the mean blood pressure of the patients in whom cotton-wool spots resolved within three months – systolic mean, 155 (range 140–170) mmHg, diastolic mean, 88 (range 75–95) mmHg – and the blood pressure of the patients in whom the lesions persisted longer – systolic mean, 148 (range 120–175) mmHg, diastolic mean, 90 (range 70–100) mmHg.

Discussion

The findings of the present study considerably extend the findings⁴ from a quantitative perimetric technique and an accurate technique for superimposing visual field data on to the corresponding fundus morphology. Retinal cotton-wool spots were consistently associated with localised non-arcuate scotomata in the visual field. Of 12 eyes which were re-examined the cotton-wool spots had disappeared within a few months in four, and in two of these the corresponding scotoma disappeared together with the morphological lesion. In the other eight eyes the cotton-wool spots (and the corresponding scotomata) persisted for more than one year.

Retinal cotton-wool spots are defined on the basis of their funduscopic appearance; typically they are white fluffy areas of retinal opacity with feathery margins. This appearance is assumed to reflect focal swelling of the nerve fibres, which is due to intracellular fluid and organelles accumulated secondary to interrupted axoplasmic flow.⁷ The aetiology of axonal disturbance at the site of the lesion is controversial, and no single explanation consistently explains the available data.⁸ It is generally believed, however, that focal retinal ischaemia is often a factor in its pathogenesis.

The natural history of the cotton-wool spots followed in the present study showed two different patterns. In one group of patients the lesions resolved within three months of the initial examination, whereas in another group the lesions persisted for more than one year. Since the age of the cotton-wool spots at the time of the initial examination is unknown, it is uncertain whether the lifetime of the lesions actually differed. If it did, however, the observed difference in natural history of the lesions might perhaps reflect differences in their pathophysiological basis. This view is supported by studies which have shown the lifetime of cotton-wool spots to vary considerably in different retinal diseases, such as for example hypertensive and diabetic retinopathy.^{8,9} The fact that no difference was found between the mean blood pressure in the two groups of patients, however, argues against raised blood pressure as a cause of the lesions in one of these groups. This view finds

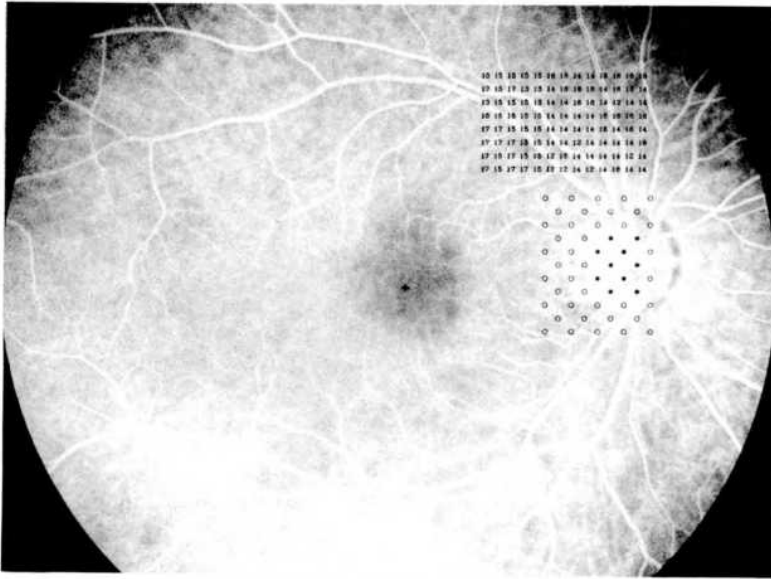


Figure 2C A fluorescein angiogram of the same eye obtained on the same day as Fig 3B, and visual field data have been superimposed. No angiographic traces of the funduscopically resolved cotton-wool spot can be seen.

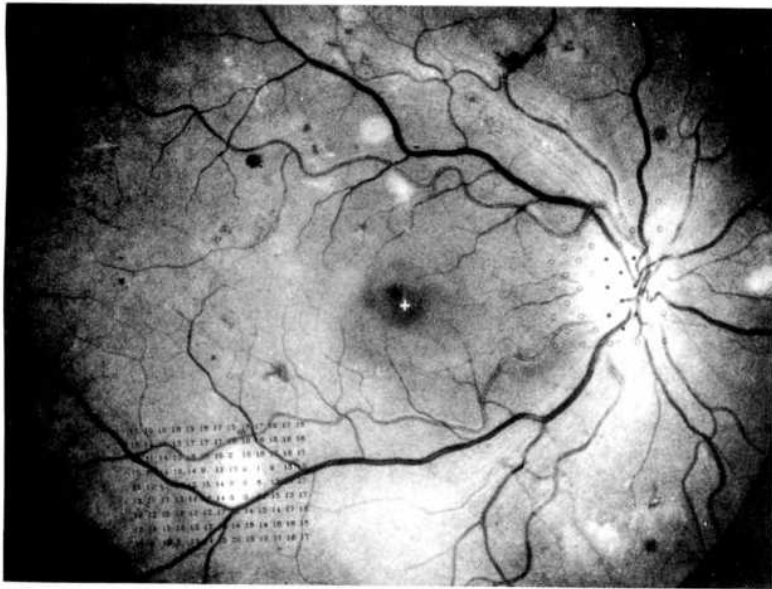


Figure 3A A right eye fundus photograph of a diabetic patient with background retinopathy of heterogeneous morphology. The perimetric stimulus pattern extended from degree co-ordinates $(x, y) = (-20, 8)$ to $(-8, 16)$. The visual field data have been superimposed on to the corresponding fundus morphology, and a scotoma in the visual field is seen to correspond to a retinal cotton-wool spot at the lower temporal branch.

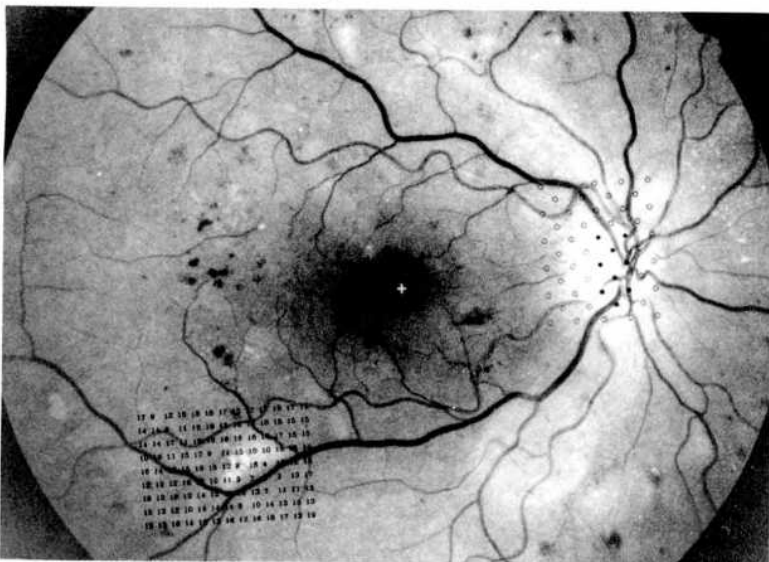


Figure 3B A fundus photograph of the same eye 12 months later. The retinal cotton-wool spot (though changed in appearance) is seen to persist together with a scotoma in the visual field (low decibel values). Other cotton-wool spots along the upper temporal arch and nasal to the optic nerve head (compare with Fig 3A) have now disappeared.

further support in a prior study that showed no correlation between blood pressure and retinal cotton-wool spots in diabetic retinopathy.¹⁰

The scotomata found in association with cotton-wool spots did not extend in an arcuate fashion within the area of the visual field tested, which would be expected if the nerve fibres traversing the lesions were injured. It thus seems that these fibres are still viable despite probably extensive structural changes at the site of the lesion. Other studies support the idea that nerve fibre function is rather resistant to the damage caused by cotton-wool spots. In one study metabolic enzyme activity was found to be preserved in nerve fibres adjacent to cotton-wool spots,¹¹ and the results of another study strongly suggest that the formation of the lesion itself requires that the axoplasmic flow of the nerve fibres is preserved.⁷ The fact that the non-functioning retinal areas corresponding to the cotton-wool spots in some cases extended beyond the peripheral aspects of the lesion remains to be explained. The finding, however, could perhaps be a parallel to evidence from experimentally produced cotton-wool spots showing that axons may penetrate some way into the lesion before swelling is seen histologically.⁷

The fact that some scotomata persisted after resolution of the cotton-wool spots probably indicates that the recorded visual loss is not always entirely due to opacity of the lesion blocking the perimetric stimulus light from reaching the retinal photoreceptors, but probably is also due to structural injury to some part of the retina. This injury is probably reflected in the persisting angiographic pathology at the site of the resolved cotton-wool spot in these cases. In some studies it has been reported that scotomata sometimes occur in the visual field of diabetic patients without any lesion in the fundus.^{12,13} These scotomata have been interpreted as an indication that neurosensory cell damage occurs before the development of morphological lesions in this disease. This interpretation, however, may easily be wrong if the scotomata represent the remaining signs of a resolved cotton-wool spot.

In conclusion, the findings of the present study show that cotton-wool spots of diabetic retinopathy cause localised non-arcuate scotomata in the visual field which may persist when the fundus lesions resolve. They indicate that the function of nerve fibres traversing the lesions is probably preserved and that small scotomata in the visual field of diabetic patients may represent the remaining signs of a resolved cotton-wool spot.

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- 1 Brown GC, Brown MM, Hiller T, Fischer D, Benson E, Magargal LE. Cotton-wool spots. *Retina* 1985; 5: 206-14.
- 2 Roy M, Rick ME, Higgins KE, McCulloch JC. Retinal cotton-wool spots: an early finding in diabetic retinopathy? *Br J Ophthalmol* 1986; 70: 772-8.
- 3 Ashton N. Pathophysiology of retinal cotton-wool spots. *Br Med Bull* 1970; 26: 143-50.

- 4 Williams DK, Drance S, Harris GS, Fairclough M. Diabetic cotton wool spots: an evaluation using perimetric and angiographic techniques. *Can J Ophthalmol* 1970; 5: 68-77.
- 5 Bek T, Lund-Andersen H. The influence of stimulus size on perimetric detection of small scotomata. *Graefes Arch Clin Exp Ophthalmol* 1989; 227: 531-4.
- 6 Bek T, Lund-Andersen H. Accurate superimposition of visual field data onto fundus pictures. *Acta Ophthalmol (Kbh)* 1990; 69: 11-8.
- 7 McLeod D, Marshall J, Kohner EM, Bird A. The role of axoplasmic transport in the pathogenesis of retinal cotton-wool spots. *Br J Ophthalmol* 1977; 61: 177-91.
- 8 Hodge JV, Dollery CT. Retinal soft exudates. A clinical study by colour and fluorescence photography. *Q J Med* 1964; 129 (N Ser 33): 117-31.
- 9 Kohner EM, Dollery CT, Bulpitt CJ. Cotton-wool spots in diabetic retinopathy. *Diabetes* 1969; 18: 691-704.
- 10 Esmann V, Lundbaek K, Madsen PH. Types of exudates in diabetic retinopathy. *Acta Med Scand* 1963; 174: 375-84.
- 11 Diezel PB, Willert HG. Morphologie und Histochemie der Harten und weichen Exsudate der Retina bei Diabetes mellitus und essentieller Hypertonie. *Klin Monatsbl Augenheilkd* 1961; 139: 475-91.
- 12 Bloom A, Heath JH, Kelsey PR, Hunter PR, Bridgden WD. The use of the Roth-Keeler central field scotometer in the study of diabetic retinopathy. *Ophthalmic Res* 1972; 3: 166-73.
- 13 Roth JA. Central visual field in diabetes. *Br J Ophthalmol* 1969; 53: 16-25.

Traumatic retinal detachment

P B Johnston

Abstract

Seventy-seven patients developed retinal breaks following an episode of ocular contusion, and 65 (84.4%) of these developed rhegmatogenous retinal detachment. Surgical treatment successfully restored or maintained retinal apposition in 74 (96.1%) of the eyes. Thirty-six (46.8%) eyes recovered visual acuity of 6/9 or better. Of the retinal breaks recognised dialysis at the ora serrata was observed in 49 eyes, of which 28 were situated at the lower temporal quadrant. Seventeen eyes had irregular breaks arising within necrotic retina at the site of scleral impact. Twenty-four (31.2%) patients had retinal break or retinal detachment diagnosed within 24 hours of injury and 49 (63.6%) within six weeks. Immediate retinal detachment was a feature of necrotic retinal breaks, while inferior oral dialyses led to a slow accumulation of subretinal fluid. Delayed diagnosis of retinal detachment was due either to opaque media or to failure to examine the retina after injury. Visual prognosis was good when retinal break or detachment were diagnosed within six weeks of injury. However, those patients who escaped initial retinal examination and were lost to follow-up had a less favourable visual outcome.

Impact of a blunt object against the eye causes direct tissue damage at the site of impact and indirect injury to distant intraocular tissues by transmitted forces. This type of contusional

trauma is a well recognised cause of rhegmatogenous retinal detachment, which was reported by Eagling¹ to affect 4.6% of such injuries. The characteristics of postcontusion retinal detachments were described by Cox *et al*² and the mechanism of break formation was elucidated by Delori *et al*³ who studied the effect of high speed projectiles on enucleated pig eyes. Experimental evidence indicates that retinal breaks form at the time of ocular impact. However, clinical reports show considerable delay in the diagnosis of post-traumatic retinal detachment. For example, Cox *et al*² reported that only 30% of post-traumatic retinal detachments were diagnosed within one month of injury, and Ross⁴ found 40% in a similar period.

The following study is of a series of patients who developed retinal breaks or retinal detachment after ocular contusion. Analysis of the results allows comment on: (1) the types of retinal breaks; (2) the time interval from injury to recognition of retinal detachment; (3) factors which limit visual recovery; (4) reason for delayed diagnosis of retinal detachment.

Patients and methods

The Retinal Clinic at the Royal Victoria Hospital, Belfast, is responsible for surgical treatment of all retinal detachments in Northern Ireland – population 1.5 million. As most cases of ocular contusion are referred as emergencies to that hospital, we are in a position to record the early characteristics of most contusional retinal detachments. From January 1980 to December 1988 we treated 77 patients who developed retinal breaks or rhegmatogenous retinal detachment which were related to a definite episode of ocular contusion. This represents 6% of 1250 consecutive cases of rhegmatogenous retinal detachment treated within this period at Belfast.

Results

Of the 77 patients 49 (63.6%) were seen at the Eye Clinic within 24 hours of injury and 64 (83%) within six weeks. Fourteen (18%) patients were seen for the first time more than six weeks after the injury. Sixty-nine (90%) were male and eight (10%) female. Their ages ranged from 5 to 69 years, mean 25.1 years. The majority of patients, 61 (79%), were injured by missiles or during sports (Table 1). The latter group consisted of 23 patients of whom 11 were injured playing association football and six from racquet sport accidents.

Of the 77 patients 65 (84.4%) developed retinal detachment and 12 (15.6%) had flat retinal breaks. Simultaneous ocular injuries included vitreous haemorrhage in 40 patients (52%) and hyphaema in 32 (42%) patients (Table 2).

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Table 1 Cause of injury

	No	%
Missiles	38	49.4
Sport	23	30.0
Assault	10	13.0
RTA*	2	2.6
Fall	3	4.0
Explosion	1	1.3
Total	77	

*Road traffic accident.

Table 2 Associated ocular injury

	No	%
Vitreous haemorrhage	40	52
Hyphaema	32	42
Lens subluxation	11	14.2
Iridodialysis	4	5.2

Table 3 Types and location of retinal breaks

	No	Upper temporal	Upper nasal	Lower temporal	Lower nasal
Ora (dialysis)	49	10	10	28	1
Impact necrosis	17	5	0	10	2
Horseshoe	7	4	3	0	0
Giant tear	3	3	3		
No tear	1				
Total	77				

The types of retinal breaks were grouped as dialyses at the ora serrata, irregular breaks within necrotic retina, horseshoe breaks, and giant tears (Table 3). Seven patients (9%) were myopic, ranging from -5.5 dioptres to -20 dioptres.

SURGICAL RESULTS AND VISUAL OUTCOME

All 77 patients were treated surgically, and of these cases 74 (96.1%) were successful. The postoperative visual recovery is summarised in Table 4, which shows that 36 patients (46.8%) saw 6/9 or better and 19 (24.7%) patients were 6/60 or worse. The causes of visual acuity of 6/60 or worse are listed in Table 5. They include seven cases in which the poor vision could be directly attributed to posterior pole trauma, consisting of choroidal tears in five patients and macular holes in two patients.

INTERVAL FROM INJURY TO DIAGNOSIS OF RETINAL DETACHMENT

The patients were divided into three groups which were determined by the interval from injury to diagnosis of the retinal break or retinal detachment (Table 6).

Group 1

This group consisted of 24 patients who developed a recognisable retinal break or rhegmatogenous retinal detachment within 24 hours of injury (Table 7). Oral dialysis or necrotic impact

Table 4 Postoperative visual acuity

	No	%
6/6-6/9	36	47
6/12-6/18	13	17
6/24-6/36	9	11.7
6/60 or less	19	24.7
Total	77	

Table 5 Causes of acuity 6/60 or worse

Choroidal tear	5
Macular pucker	2
Macular hole	2
Proliferative vitreopathy	3
Chronic retinal detachment preop	6
Amblyopia	1
Total	19

Table 6 Interval from injury to diagnosis of retinal break of detachment

Group	Interval	No	%
1	<1 day	24	31.2
2	1 day-6 weeks	25	32.5
3	6 weeks-6 months	18	23.4
	6 months-1 year	5	6.5
	>1 year	5	6.5
Total		77	

Table 7 Types of retinal breaks and incidence of retinal detachment within one day of injury

Type	No	Associated RD
Impact necrosis	10	8
Ora (dialysis)	10	4
Horseshoe	2	0
Giant tear	2	2
Total	24	14

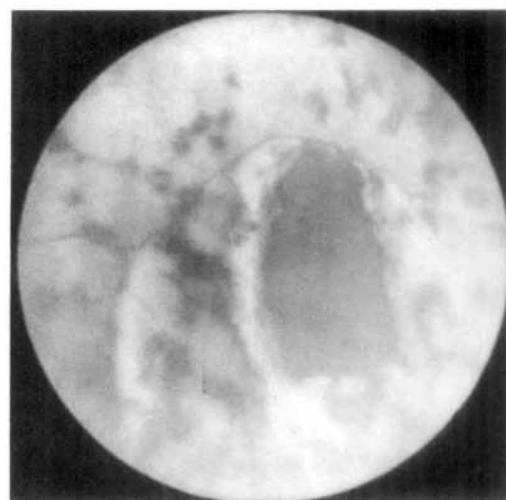


Figure 1: Inferotemporal fundus of left eye contains an oval retinal tear surrounded by oedematous and haemorrhagic retina, which is detached.

breaks accounted for the majority of breaks in this group, but it was noticeable that the necrotic type was more often associated with detachment. Fluorescein angiography was performed on a number of patients with necrotic breaks. This consistently showed non-perfusion of the oedematous retina round the break and profuse leakage of fluorescein through damaged retinal pigment epithelium into the subretinal space (Figs 1, 2).

Group 2

This group consisted of 25 patients who had a break or rhegmatogenous retinal detachment which was diagnosed between one day and six weeks after the injury (Table 8). Most of the breaks were oral dialyses which affected 13 (52%) patients, of which 11 patients had retinal detachment and two had dialyses without detachment. The diagnosis of detachment or break was delayed in this group of patients for the following reasons: (1) vitreous haemorrhage prevented immediate postinjury examination of the peripheral retina in 10 patients; (2) referral to

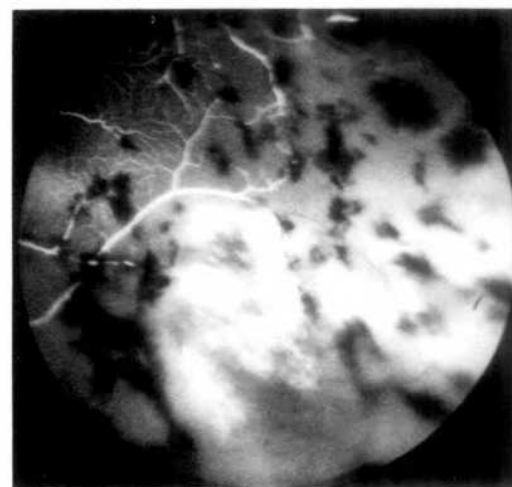


Figure 2: Fluorescein angiogram of fundus shown in Figure 1. There is gross retinal vascular stasis and ischaemia round the retinal tear and leakage of dye from the choroidal vasculature beneath the tear.

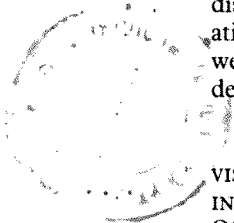
Table 8 Types of retinal break and incidence of retinal detachment one day to six weeks after injury

Type	No	Associated RD
Ora (dialysis)	13	11
Impact necrosis	7	7
Horseshoe	4	4
Giant tear	1	1
Total	25	23

hospital was delayed in seven patients; (3) nine patients did not attend until retinal detachment caused loss of vision.

Group 3

This group consisted of 28 patients with oral dialyses who presented with loss of vision caused by retinal detachment more than six weeks after the injury. The time interval from injury to diagnosis of retinal detachment ranged from two months to four years, mean 9.7 months. Of these 28 patients 15 were examined in the Eye Department within 24 hours of injury and the visual acuity was recorded. Vitreous haemorrhage was noted in 12 and hyphaema in 14 of these 15 eyes. However, retinal detachment was not diagnosed until the patient returned with visual loss caused by the detached retina. Delayed diagnosis of these 15 patients probably contributed to a permanently reduced acuity of more than three lines Snellen in 11 eyes which might otherwise have maintained normal vision. The presence of vitreous haemorrhage, hyphaema, and ocular discomfort had prevented immediate examination of the peripheral retina. These 15 patients were lost to follow-up until retinal detachment developed.



VISUAL RECOVERY AND INJURY TO DIAGNOSIS INTERVAL

Of the 24 patients (group 1) diagnosed within 24 hours of injury, 16 (66%) regained 6/9 vision or better and in four (16%) the visual acuity was 6/60 or worse.

Group 2 consisted of 25 patients who were diagnosed from one day to six weeks after the injury. Of these, 17 (68%) regained 6/9 vision or better and in 5 (20%) the visual acuity was 6/60 or worse. Visual acuity of 6/60 and worse was usually caused by direct macular injury in both group 1 and group 2.

The third group of 28 patients were diagnosed more than six weeks after injury, and of these, 5 (18%) regained 6/9 vision or better and in 9 (32%) the visual acuity was 6/60 or worse. Poor recovery of vision in group 3 patients was caused by chronic retinal detachment in every case.

Discussion

Retinal tears may occur in young healthy eyes after blunt injury. We treated 77 patients with retinal tear or rhegmatogenous retinal detachment which followed a documented episode of ocular contusion. In 63.6% of cases the retinal break, excluding giant tears, was found at the ora, which compares with an incidence of 59.4% reported by Cox *et al*² but is more than the 53% observed by Goffstein and Burton.⁵ Cox *et al* did

not report giant tears in their series of contusional retinal detachment, but Goffstein and Burton found a 16% incidence of these tears. We observed three (4%) giant tears, and two of these were in myopic eyes of -16.0 and -20.0 dioptres, which supports the view⁵ that highly myopic eyes are at increased risk of giant tear formation following ocular contusion. We found that 57% of oral breaks affected the inferior temporal quadrant, which is the usual site of scleral impact. Cox *et al*² observed that the inferior temporal quadrant was less often involved (22%) and the upper nasal quadrant predominantly affected (37.8%). Seventeen eyes in our series contained irregular breaks within oedematous haemorrhagic retina at the point of scleral impact, which is usually the inferior temporal quadrant. Necrotic breaks were extensively described by Cox⁶ and represent impact retinal necrosis, which is a consequence of direct concussion damage to the retina, and retinal vascular damage, which includes vasoconstriction and disintegration of capillary walls.⁷ Fluorescein angiography of these tears revealed striking retinal ischaemia and outpouring of fluid in the region of the tear. Gregor and Ryan⁸ and Cox⁶ showed experimentally that disruption of the retinal pigment epithelium occurs at the impact site immediately after blunt injury, and fluorescein angiography performed within 24 hours of injury in our cases confirmed profuse leakage through the damaged retinal pigment epithelium into the subretinal space. Development of retinal detachment within 24 hours of injury was a feature of necrotic retinal breaks in comparison with oral dialysis, and we suggest that leakage of fluid from the choroid into the subretinal space contributes to development of retinal detachment in addition to movement of vitreous fluid through the retinal break. Eight patients developed horseshoe tears at the site of pre-existing vitreoretinal degeneration as a consequence of sudden vitreous traction caused by deformation of the globe.²

Classic laboratory experiments^{3,9} show that retinal breaks responsible for traumatic retinal detachment are formed at the time of injury. The observation is difficult to confirm clinically, as patients who develop traumatic retinal detachment rarely present for peripheral retinal examination immediately after the injury. For example Cox *et al*² reported that 12% of traumatic breaks or retinal detachments occurred immediately and 30% within one month of injury. Goffstein and Burton⁵ observed that 60% were diagnosed within eight months of injury. We were unable to confirm the experimental evidence and found that, although 49 patients were examined within 24 hours of injury, the retinal break or rhegmatogenous retinal detachment was recognised in only 24 eyes. In the remaining 25 patients diagnosis was unduly delayed for two reasons: (1) vitreous haemorrhage or hyphaema prevented early examination of the peripheral retina; and (2) 15 patients were not examined immediately after the injury by the retinal service and were lost to follow-up.

Analysis of the types of retinal breaks in our series shows that necrotic breaks, horseshoe breaks, and giant tears develop retinal detach-

ment within six weeks of injury. Oral dialyses were more likely to be associated with delayed accumulation of subretinal fluid^{4,10} which spread slowly until the macular region was detached.⁷ If a retinal dialysis is unrecognised within six weeks of injury, these patients usually present with loss of vision within one year of injury, though a few present up to four years later.

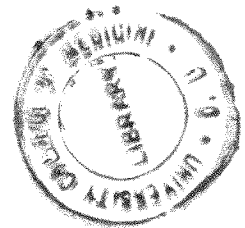
Surgical reattachment of the retina was successful in 96% of eyes. The major causes of poor visual recovery were either chronic pre-operative detachment of the macula or posterior pole contusional injury such as choroidal tear of lamellar hole at the macula. Patients diagnosed within six weeks of injury showed better visual recovery than those detected later, which reflects the more extensive retinal detachment associated with the latter cases. Overall, 47% of patients regained visual acuity of 6/9 or better following surgery and 24.7% were 6/60 or worse. The visual recovery compares favourably with other reports, which found visual acuity of 6/60 or worse in 32% of cases.^{4,11}

Our experience emphasises the great importance of frequent and early examination of the retinal periphery after ocular trauma if vision is to be preserved. When vitreous haemorrhage or

hyphaema obscures the view, the patient should be frequently re-examined until a complete view of the ora serrata is obtained.

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- 1 Eagling EM. Ocular damage after blunt trauma to the eye. *Br J Ophthalmol* 1974; 58: 126-40.
- 2 Cox MS, Schepens CL, Freeman HM. Retinal detachment due to ocular contusion. *Arch Ophthalmol* 1966; 76: 678-85.
- 3 Delori F, Pomerantzeff O, Cox MS. Deformation of the globe under high speed impact: its relation to contusion injuries. *Invest Ophthalmol Vis Sci* 1969; 3: 290-301.
- 4 Ross WH. Traumatic retinal dialyses. *Arch Ophthalmol* 1981; 99: 1371-4.
- 5 Goffstein R, Burton TC. Differentiating traumatic from non-traumatic retinal detachment. *Ophthalmology* 1982; 89: 361-8.
- 6 Cox MS. Retinal breaks caused by blunt non-perforating trauma at the point of impact. *Trans Am Ophthalmol Soc* 1980; 78: 414-66.
- 7 Duke-Elder S. Concussions and contusions. *System of ophthalmology*. London: Kimpton, 1972; 14 (1): ch2 63-310.
- 8 Gregor Z, Ryan SJ. Blood-retinal barrier after blunt trauma to the eye. *Graefes Arch Clin Exp Ophthalmol* 1982; 219: 205-8.
- 9 Wiedenthal DT, Schepens CL. Peripheral fundus changes associated with ocular contusion. *Am J Ophthalmol* 1966; 62: 465-77.
- 10 Hagler WS, North AW. Retinal dialysis and retinal detachment. *Arch Ophthalmol* 1968; 79: 376-88.
- 11 Tasman W. Retinal dialysis following blunt trauma. In: Freeman HM, ed. *Ocular trauma*. New York: Appleton-Century-Crofts, 1979; 295-9.



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Lectin binding sites in normal, scarred, and lattice dystrophy corneas*

P N Bishop, R E Bonshek, C J P Jones, A E A Ridgway, R W Stoddart

Abstract

Normal, scarred, and dystrophic corneas were histochemically probed with a panel of 16 lectins by means of an avidin-biotin revealing system. Normal corneal epithelial cells, keratocytes, and endothelial cells expressed at least two distinct N-linked oligosaccharide subsets, of the non-bisected, biantennary and bisected, bi-/triantennary types. Corneal scars stained variably with the lectin subsets described above, and with *Maclura pomifera* agglutinin. Lattice dystrophy corneas showed a loss of the oligosaccharide expression observed on the plasma membranes of normal epithelial cells, and there was concurrent deposition of extracellular glycoprotein within the corneal stroma, which was of the same oligosaccharide subsets as were lost from the epithelial cell plasma membranes. This extracellular stromal glycoprotein was far more widely deposited than the amyloid and extended well beyond the stromal scarring. We propose that these observations are related and that in lattice corneal dystrophy a glycoprotein(s) is shed from the plasma membranes of epithelial cells and sequestered within the corneal stroma, where it subsequently stimulates amyloid deposition.

Lattice corneal dystrophy type 1 is an autosomal dominant condition¹ causing progressive bilateral corneal opacities typified by lattice lines. Histologically the lattice lines have the staining characteristics of amyloid.² Previous studies, including studies in lectin histochemistry, have demonstrated 'abnormal' extracellular material within the corneal stroma apart from the amyloid,^{3,4} while electron microscopic techniques have identified a similar 'abnormal' material between and beneath the basal epithelial cells.^{3,5} However, the relationship between this material, the amyloid deposits, and underlying cellular mechanisms has not been clearly defined.

As lectins are known to bind to the extracellular deposits of lattice corneal dystrophy, including the amyloid,⁴ and they have an affinity for cellular oligosaccharides, a panel of lectins was used histochemically to probe corneas with this condition. Normal corneas were examined, as their binding to the lectins used in this study was previously only partially defined.^{6,7} A pathological sequel of lattice corneal dystrophy is scarring. We therefore examined corneas with scarring arising from a variety of other causes, in

order to establish the contribution of scarring to the observed lectin binding pattern in lattice corneal dystrophy.

Materials and methods

Four normal corneas were obtained from eyes enucleated for malignant melanoma of the choroid (patients' ages 38-73 years). Six scarred corneal buttons were obtained at penetrating keratoplasty following trauma, trachoma, interstitial keratitis, herpes simplex keratitis, and one with longstanding scarring of uncertain cause. Twelve corneal buttons were obtained from patients (aged 25-90 years), these were histologically diagnosed as lattice dystrophy corneas. Seven of these corneas were from four distinct pedigrees with the classical clinical signs and an autosomal dominant family history characteristic of type 1 lattice dystrophy.¹ The other five histologically diagnosed buttons came from patients in whose case notes a family history was not recorded, so that it was not possible to give an unequivocal diagnosis of the type 1 variety.

All specimens were immediately fixed in 10% (v/v) neutral formalin buffered with 0.1 M phosphate buffer, and cetylpyridinium chloride (CPC) 0.1% (w/v), pH 7.4, for 16 to 24 hours, prior to dehydration and embedding in paraffin wax. Each cornea underwent conventional histological examination, including staining with haematoxylin and eosin, Congo red, and the periodic acid-schiff (PAS) reaction.

For lectin histochemistry, sections were cut at 4 µm, mounted on poly-L-lysine coated slides, and treated with biotinylated lectin followed by avidin peroxidase conjugate. A biotinylated lectin is a lectin to which biotin has been synthetically coupled. The biotin can then act as a reporter molecule which is specifically detected by interaction with avidin or streptavidin. The avidin used here is chemically coupled to the enzyme horseradish peroxidase, which in turn is revealed by interaction with DAB (diaminobenzidine tetrahydrochloride dihydrate). This revealing system is extremely sensitive and specific, ultimately resulting in the dense brown stain of DAB corresponding to areas of lectin binding.

Biotinylated lectins, avidin peroxidase conjugate, and crude trypsin (type II from porcine pancreas), were obtained from Sigma, Poole, Dorset, UK. The lectins used in this study were those of Jack bean (*Canavalia ensiformis*, con A), garden pea (*Pisum sativum*, PSA), common lentil (*Lens culinaris*, LCA), kidney bean (*Phaseolus vulgaris*, type III, erythroagglutinin, e-PHA), and type IV leucoagglutinin, l-PHA), wheat germ (*Triticum vulgaris*, WGA), pokeweed (*Phytolacca*

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Table 1 Lectin staining in normal and lattice dystrophy corneas: comparison of basal epithelial cells and stroma (averaged results for all normal and lattice dystrophy corneas)

	Lectins					
	Con A	PSA	LCA	ePHA	WGA	MPA
<i>Normal Cornea</i>						
Basal epithelial cells						
Plasma membrane	++	+++	+++	+++	+++	-
Cytoplasmic granules	+++	++	++	++	++	-
Nuclear envelope	++	-	-	-	-	-
Cytoplasm background	+	+/-	+/-	-	-	-
Stroma						
Background	+	+	+	-	-	-
<i>Lattice dystrophy cornea</i>						
Basal epithelial cells*						
Plasma membrane	+/-	+/-	+/-	+/-	+/-	-
Cytoplasmic granules	++	+	+	+	+	-
Nuclear envelope	++	-	-	-	-	-
Cytoplasm background	+	+/-	+/-	-	-	-
Stroma						
Background	+	+	+	-	-	-
Extracellular deposits†	+++	+++	+++	+++	+++	-
Amyloid (lattice lines)	+	+	+	+	+	-
Scarring (where stained)	+++	+++	+++	+++	+++	+

Scoring: absent = -, faint or equivocal = +/-, up to heavy staining = +++. *Excluding areas with disrupted epithelial architecture, see text. †Extracellular deposits excluding amyloid and scarring.

americana, PAA), soybean (*Glycine max*, SBA), peanut (*Arachis hypogaea*, AHA), hairy vetch (*Vicia villosa*, VVA), *Bandeiraea simplicifolia* isolectin 1-B4 (BSA), asparagus or winged pea (*Tetragonolobus purpureus*, LTA), gorse (*Ulex europaeus* isolectin 1, UEA), osage orange (*Machura pomifera*, MPA), horse gram (*Dolichos biflorus*, DBA) and edible snail (*Helix pomatia*, HPA). All were used as biotinylated derivatives, and showed competitive inhibition with appropriate monosaccharides, apart from e-PHA and l-PHA, which do not show monosaccharide inhibition.⁸

A standard lectin staining procedure was used.⁹ The sections were dewaxed in xylene and then transferred to absolute alcohol. Endogenous

peroxidase activity was blocked with 0.5% (v/v) hydrogen peroxide in absolute methanol containing 0.4% (v/v) 1 N hydrochloric acid for 30 minutes at 18°C, and then the sections were washed in 0.05 M Tris buffered saline (TBS), pH 7.6. Trypsinisation was carried out at 37°C for 10 minutes with crude trypsin (Sigma type II), to expose sugar residues occluded by fixation.¹⁰ After being washed in TBS the sections were incubated at 18°C with 10 mg/l biotin labelled lectin in 0.05 M TBS, pH 7.6, with 1 mM CaCl₂ for 30 minutes. Control sections were included in each run, which were treated identically apart from being incubated in buffer alone at this stage. All sections were washed in TBS containing 1 mM CaCl₂ and placed in 5 mg/l avidin-peroxidase in 0.125 M TBS (containing 0.347 M NaCl) for 1 hour. The sections were jet washed in TBS (0.05 M) and incubated in a solution of 0.05% (v/w) DAB (Aldrich Chemical Co., Gillingham, UK), 0.05 M TBS and 0.015% (v/v) hydrogen peroxide for 5 minutes at room temperature. They were counterstained with 0.25% (w/v) methyl green in 0.1 M sodium acetate buffer (pH 4.8), before being dehydrated and mounted in DePeX. Photography was performed on an Olympus BH-2 photographic microscope, with an Olympus OM PM-10AD photomicrographic system. The film used was Kodak Panatomic-X.

Results

Each group of corneas (normal, scarred, and lattice dystrophy) produced consistent lectin binding patterns, except where stated. The four



Figure 1 Normal cornea stained with LCA. Basal epithelium shows staining of plasma membranes, and cytoplasmic granules. This section also shows staining of the epithelial basement membranes and Bowman's membrane. There is staining of the keratocytes and pale background stromal staining. (×280.)

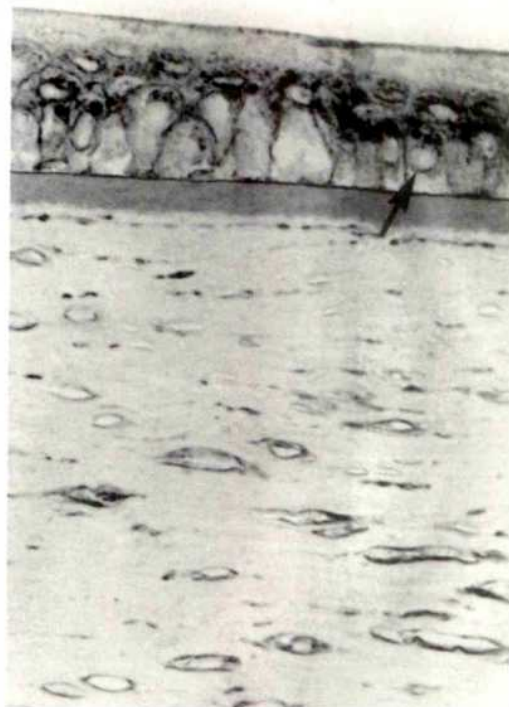


Figure 2 Normal cornea stained with con A. Same section as Fig 1 showing similar staining to LCA, but also staining of epithelial nuclear envelope (arrow) and diffuse cytoplasmic staining. (×280.)

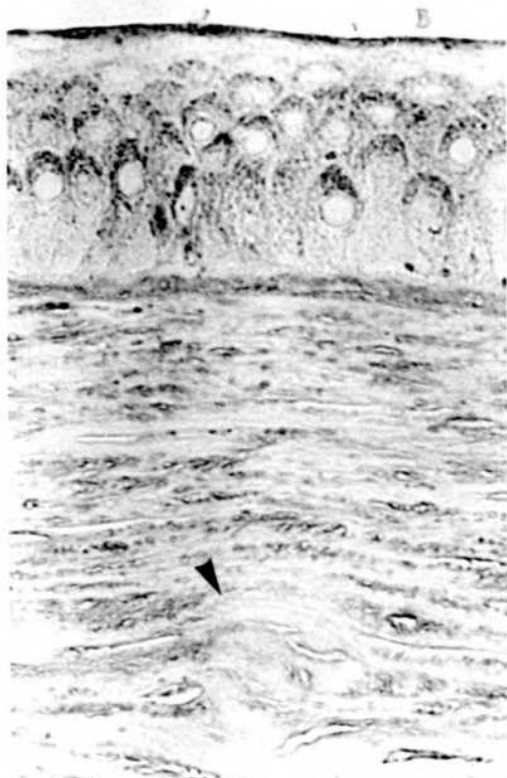


Figure 3 Lattice dystrophy cornea stained with con A. There is a loss of epithelial cell plasma membrane (surface membrane) staining highlighted by preservation of cytoplasmic granular staining. Nuclear envelope staining is preserved. The anterior stroma has extensive densely staining extracellular stromal deposits and also a lightly staining lattice line which is difficult to distinguish above normal background staining (arrow). ($\times 560$.)

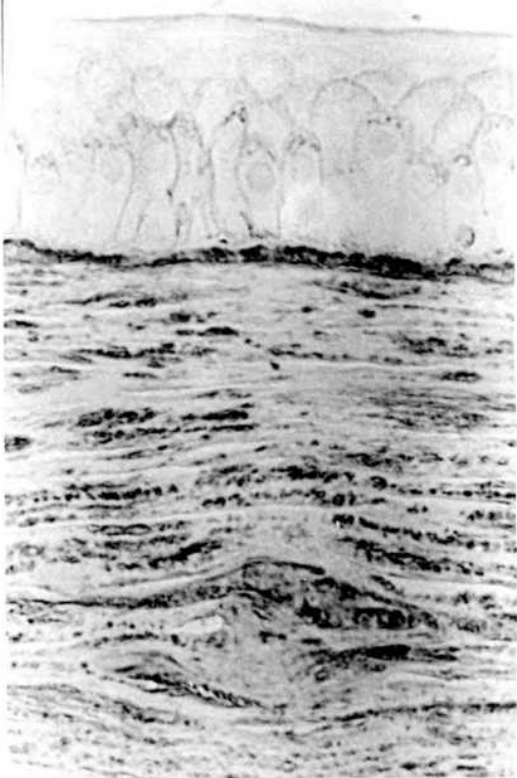


Figure 4 Lattice dystrophy cornea stained with PSA. Same specimen as Fig 3, with marked reduction in epithelial cell plasma membrane staining and reduced, but still visible cytoplasmic granular staining. ($\times 560$.)

normal corneas all showed staining of their epithelial cells, keratocytes, and endothelial cells with the lectins con A, PSA, LCA, e-PHA, and WGA. The epithelium had strong staining of its basal and inner wing cell layers with all of these lectins (Table 1), but had progressively less staining of the more superficial layers. The staining was localised to the plasma membrane (the surface membrane bounding the cell) and to cytoplasmic granules, which were predominantly apical in the basal cells, with all these lectins (Fig 1), except con A, which also stained the nuclear envelope strongly and produced weak diffuse staining of the cytoplasm (Fig 2). The anterior surface of the cornea stained strongly with these lectins and stained faintly with l-PHA. Through lack of resolution at the light microscopic level it

was difficult to determine the distribution of staining within the keratocytes and endothelial cells. The normal corneal epithelial cell basement membrane and Bowman's membrane variably stained with con A, PSA, LCA, e-PHA, and WGA. This staining, when present, was pale and often inconstant along the length of the membranes. The corneal stroma demonstrated diffuse pale staining with con A, PSA, and LCA. No staining of Descemet's membrane was observed. None of the other lectins in the panel stained normal corneas.

All six scarred corneas had a similar lectin binding pattern to normal corneas, except in the zones of stromal scarring and, sometimes, in localised areas of overlying disorganised epithelium. Stromal scar tissue showed two distinct patterns, either heavy staining with the lectins con A, PSA, LCA, e-PHA, WGA and moderate staining with the lectin MPA, or zones

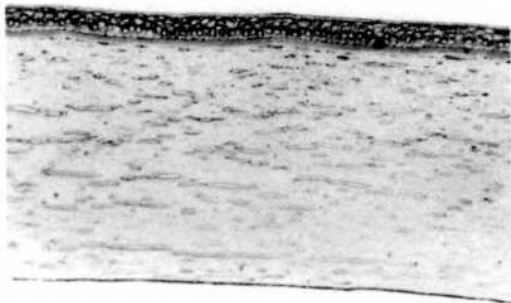


Figure 5A

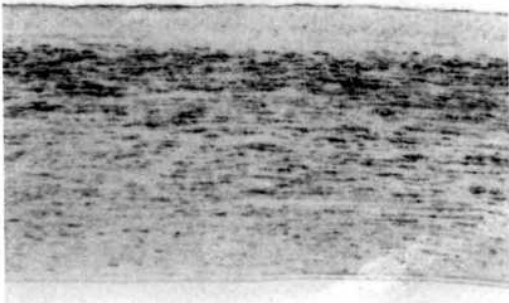


Figure 5B

Figure 5 A, B: Comparison of normal (A) and lattice dystrophy (B) corneas stained with con A. The lattice dystrophy cornea has a marked loss of epithelial cell plasma membrane staining, with a concurrent deposition of stainable extracellular material within the anterior stroma. ($\times 32$.)



Figure 6 Lattice dystrophy cornea stained with con A. This shows similar features to Fig 4, with preservation of staining of the nuclear envelope but a more marked loss of cytoplasmic granular staining. A band of staining is clearly visible superficial to the epithelial basement membrane (arrow). ($\times 420$.)

where the lectin staining was absent. These unstained zones corresponded to hyalinised patches seen on haematoxylin and eosin staining. The overlying epithelium showed inconstant lectin labelling, which was variably normal, increased, or absent. If staining was absent there was a total loss of lectin binding, including the binding of con A to the nuclear envelope.

All twelve corneas with lattice corneal dystrophy showed a similar lectin binding pattern. They gave morphological evidence of superficial stromal scarring – that is, disruption of the collagenous architecture – which produced the same staining patterns as observed in the group of scarred corneas, including focal MPA staining when scarring was prominent. The amyloid of the lattice lines stained with the lectins con A, PSA, LCA, e-PHA, and WGA (Table 1). This staining was generally weak and diffuse (Figs 3 and 4). All the dystrophic samples had extensive extracellular staining of the corneal stroma, which was most dense anteriorly and centrally, including and extending beyond the areas of scarring and amyloid deposition (Figs 3, 4, and 5A, B). Similar extracellular staining was variably seen between the basal epithelial cells and their basement membrane and between the basement membrane and Bowman's membrane (where the latter was preserved). In some instances this staining was of thickly deposited masses of extracellular material (Figs 3, 4, 6); such a pattern was never seen in corneal buttons with scarring alone.

The epithelial plasma membranes of lattice dystrophy corneas showed a generalised loss of staining as compared with normal corneas (which stained with con A, PSA, LCA, e-PHA, and WGA). There was, however, preservation of

staining of cytoplasmic granules (albeit reduced) (Figs 3 and 4) and the nuclear envelope staining with con A (Figs 3 and 6) (Table 1). This contrasted with the complete loss of staining of all cellular components seen in the disorganised epithelium of some corneas with scarring alone. The anterior corneal surface, Descemet's membrane, and the endothelium all had the same staining characteristics as normal cornea. Keratocytes were difficult to identify because of the dense stromal staining.

It was notable that, in lattice dystrophy corneas, the loss of staining of architecturally normal epithelium was accompanied by an accumulation of stainable material within the subjacent regions of corneal stroma and immediately above and below the epithelial basement membrane. This stainable material extended well beyond any anterior stromal scarring and associated overlying epithelial disorganisation, which was variably seen in these specimens.

None of the corneas studied (normal, scarred, or lattice dystrophy) showed staining with the lectins PAA, SBA, AHA, VVA, BSA, LTA, UEA, DBA, and HPA.

Discussion

Corneas with lattice corneal dystrophy frequently show at least incipient scarring, hence the necessity to make comparisons with corneas scarred from other causes as well as normal corneas. The features which were peculiar to dystrophic corneas and which could not be attributed to scarring were: (1) extensive reduction, or total loss, or staining of epithelial cell plasma membranes, without marked loss of staining of their contents; (2) coextensive increase in staining of the superficial corneal stroma with, in some cases, the appearance of amorphous, stained deposits above and beneath the epithelial basement membrane; and (3) deposition of focal amyloid deposits within the corneal stroma. Stromal scarring, however, though associated with similar lectin staining (apart from also staining with MPA), had a different distribution and no clear association with epithelial change. The corneal epithelium superficial to scarring sometimes showed a highly focal loss of staining associated with architectural disruption. This involved all intracellular structures and may represent a focal loss of permeability to macromolecular reagents.

Lectins are proteins or glycoproteins, usually of plant origin, which have the property of binding to specific subsets of oligosaccharides (short sugar chains, which if N-linked contain about 12 to 24 monosaccharide units). Oligosaccharides are the saccharide component of 'classical' glycoproteins, glycolipids, and are present on core proteins of proteoglycans. Oligosaccharides destined for the cell plasma membrane and extracellular matrix components are variously synthesised within the endoplasmic reticulum and then Golgi apparatus of the cell.¹¹ They are broadly divided into two groups based on the chemical structure of the protein/sugar linkage region. These are the N-linked and O-linked varieties. The N-linked oligosaccharides can then be further defined by their typical types

of branching structure (bi- and triantennary, and bisected and non-bisected) and by their outer monosaccharide sequences (the inner monosaccharide sequences being relatively constant).

From the known binding characteristics of the panel of lectins used in this study, some tentative conclusions as to oligosaccharides expressed can be derived, as follows. PSA and LCA bind strongly to non-bisected, bi- or triantennary, complex, N-linked oligosaccharides. They also bind more weakly to high mannose and intermediate, non bisected, N-linked oligosaccharides.¹²⁻¹⁵ Con A binds to high mannose, intermediate, and small biantennary, complex N-linked oligosaccharides whether bisected or not.^{13 16-19} WGA has more varied binding capabilities, since it can interact strongly with di-N-acetyl chitobiosyl sequences, some N-acetyl lactosamine sequences and, more weakly, with some sialyl residues.²⁰⁻²³

1-PHA binds selectively to tri- and tetra-antennary, non-bisected oligosaccharides.^{13 24} We failed to demonstrate any binding with 1-PHA (apart from faint staining of the anterior corneal surface), but binding was observed with PSA and LCA, thus implying that the saccharides that bind PSA and LCA are probably biantennary and not triantennary. A similar phenomenon has been found in mast cell granules.^{25 26} e-PHA has an obligate requirement for bisected bi- or triantennary oligosaccharides^{24 27} and therefore binds to different structural subsets from PSA, LCA, and 1-PHA. e-PHA has some overlap with con A. None of the corneas examined had evidence of highly branched N-linked saccharides, except at the anterior corneal surface.

The lack of staining with the other lectins in the panel implies that L-fucose, α -D-N-acetylgalactosamine and the α and β anomers of D-galactose were generally absent as non-reducing terminal sugars, either in N-linked or O-linked saccharides. Because N-linked saccharides were demonstrably present, the implication is that they were probably terminally sialylated. While there was no direct evidence for the presence of O-linked saccharides, their occurrence could not be excluded.

The normal corneal epithelial plasma membrane and cytoplasmic granules expressed at least two subsets of N-linked oligosaccharides. These were the non-bisected bi-antennary and the bisected bi-/triantennary types. The predominance of oligosaccharide expression on the basal epithelial cells has previously been demonstrated in normal rat corneas.²⁸ The keratocytes and endothelial cells carried similar oligosaccharide subsets. The nuclear envelope and cytoplasm of the epithelial cells specifically expressed putative 'high mannose' saccharides. The extracellular matrix of the normal corneal stroma also expressed α -D-mannose particularly in the form of bi-/triantennate N-linked complexes. This may represent binding to proteoglycan core, collagen, or collagen-related oligosaccharides.

Corneal stromal scars expressed non-bisected biantennary and bisected bi-/triantennary saccharides. They also stained with MPA which has an affinity for α -D-galactose, and N-acetyl α -D-galactosamine.²⁹ Since there was no binding of

SBA, VVA, DBA, or HPA, it is unlikely that MPA was interacting with α -N-acetyl-D-galactosamine, while the lack of staining with BSA argues against a binding via α -D-galactose (though we have observed a similar disparity in other tissues). The precise mechanism of the staining with MPA is therefore uncertain, though it is possibly binding to a saccharide on collagen or an associated glycoprotein of corneal scar tissue.

In the dystrophic corneas the lectins showed reduced or absent binding to the epithelial cell surfaces, thus implying defective synthesis or loss of plasma membrane oligosaccharide. The same lectins, and hence the same oligosaccharide subsets, were expressed in deposits within the subjacent stroma, suggesting, but not proving, that the two phenomena might be related. Panjwani *et al*⁴ found a similar stromal binding pattern with con A, WGA, and RCA-1 using paraffin section, but did not comment on epithelial lectin binding.

We suggest that glycoprotein is shed from the epithelial cells and then passes through the cornea to become sequestered, predominantly within the anterior corneal stroma. The glycoprotein is retarded by the epithelial basement membrane, which is known to act as a semi-permeable filter³⁰ and Bowman's layer, resulting in the accumulation of stainable material at these anatomical interfaces. We further hypothesise that the glycoprotein, or some fragment of it, subsequently stimulates focal amyloidogenesis (amyloid production essentially involves focal nidation which once started is self-perpetuating).³¹ It is likely that this step involves the handling of the glycoprotein by keratocytes with subsequent injury to them, as intracytoplasmic material has been demonstrated within keratocytes adjacent to the amyloid deposits,²³ and degenerate keratocytes are reported in these areas.² Some part of the amyloid deposit could derive from the keratocytes rather than the epithelial glycoconjugate, since corneal scars of various origins can occasionally contain amyloid.³²

This hypothesis accords with the clinical characteristics of type 1 lattice corneal dystrophy. It begins in childhood, the first clinical sign being subepithelial corneal opacities.³³ There is usually a history of recurrent corneal erosions at this stage, suggesting an early defect at the level of the corneal epithelial plasma membrane or basement membrane. Later a diffuse anterior stromal haze develops,³³ which may represent the diffusion of glycoprotein into the corneal stroma and the extensive extracellular lectin staining seen in lattice dystrophy corneas. All these changes occur well before the classical amyloid-containing stromal lattice lines appear, suggesting that the deposition of amyloid is not a primary phenomenon. Amyloidogenesis within the corneal stroma is an occasional response to a variety of insults, including trichiasis, previous trauma, keratoconus, and granular corneal dystrophy.^{32 34-36} In lattice corneal dystrophy the abnormal presence of a diffusible glycoprotein, derived from the corneal epithelial plasma membranes, may be another such insult; but one which results in a particularly marked degree of amyloid deposition.

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- 1 Kivlin J, Lovrien EW, Maumenee IH, Bishop DT, Biss W. Linkage analysis in lattice corneal dystrophy. *Am J Med Genet* 1984; 19: 387-90.
- 2 Klintworth GK. Lattice corneal dystrophy. An inherited variety of amyloidosis restricted to the cornea. *Am J Pathol* 1967; 50: 371-99.
- 3 de Felice GP, Carta S. Lattice dystrophy of the cornea. A clinical and histopathological study. *Ophthalmologica* 1986; 192: 135-42.
- 4 Panjwani N, Rodrigues M, Free K, Krachmer JH, Albert D, Baum J. Lectin receptors of amyloid in corneas with lattice dystrophy. *Arch Ophthalmol* 1987; 105: 688-91.
- 5 Wittebol-Post D. *Corneadystrofien Op 'Nieuw' Belicht*. Dordrecht: ICG Printing, 1987: 135-42.
- 6 Panjwani N, Moulton P, Alroy J, Baum J. Localisation of lectin binding sites in human, cat, and rabbit corneas. *Invest Ophthalmol Vis Sci* 1986; 27: 1280-4.
- 7 Brandon DM, Nayak SK, Binder PS. Lectin binding patterns of the human cornea. Comparison of frozen and paraffin sections. *Cornea* 1988; 7: 257-66.
- 8 McMahon RFT, Benbow HW, Lofthouse AK, Stoddart RW. Human salivary gland glycoconjugates: a lectin histochemical study. *Histochem J* 1989; 21: 663-74.
- 9 Jones CJP, Mosley SM, Jeffrey IJM, Stoddart RW. Elimination of non-specific binding of avidin to tissue sections. *Histochem J* 1987; 19: 264-8.
- 10 Jeffrey IJM, Mosley SM, Jones CJP, Stoddart RW. Proteolysis and lectin histochemistry. *Histochem J* 1987; 19: 269-75.
- 11 Darnell J, Lodish H, Baltimore D. *Molecular cell biology*. New York: Scientific American Books, 1986: 957-64.
- 12 Trowbridge IS. Isolation and chemical characterisation of a mitogenic lectin from *Pinus sativum*. *J Biol Chem* 1984; 259: 6004-12.
- 13 Debray H, Decont D, Strecker G, Spik G, Montreuil J. Specificity of twelve lectins towards oligosaccharides and glycopeptides related to N-glycosylproteins. *Eur J Biochem* 1981; 117: 41-55.
- 14 Kornfeld K, Reitman ML, Kornfeld R. The carbohydrate binding specificity of pea and lentil lectins. Fucose is an important determinant. *J Biol Chem* 1981; 256: 6633-40.
- 15 Debray H, Montreuil J. Structural basis for the affinity of four insolubilised lectins, with a specificity for α -D-mannose, towards various glycopeptides with the N-glycosylamine linkage and related oligosaccharides. *J Bioscience* 1983; 5: 93-100.
- 16 Goldstein IJ, Hayes CE. The lectins: carbohydrate binding proteins of plants and animals. *Adv Carbohydr Chem Biochem* 1978; 35: 128-340.
- 17 Goldstein IJ, Iyer RN, Smith EE, So LL. Protein carbohydrate interaction XX. The interaction of concanavalin A with sophorose and some of its derivatives. *Biochemistry* 1967; 6: 2373-7.
- 18 Goldstein IJ, Cifonelli JA, Duke J. Interaction of concanavalin A with capsular polysaccharide of the pneumococcus type XII and isolation of kojibiose from the polysaccharide. *Biochemistry* 1974; 13: 867-70.
- 19 Kornfeld R, Ferris C. Interaction of immunoglobulin glycopeptides with concanavalin A. *J Biol Chem* 1975; 250: 2614-9.
- 20 Allen AK, Neuberger A, Sharon N. The purification, composition, and specificity of wheat germ agglutinin. *Biochem J* 1973; 131: 155-62.
- 21 Bhavanandan VP, Katlic AW. The interaction of wheat germ agglutinin with sialoglycoprotein. *J Biol Chem* 1979; 254: 4000-8.
- 22 Gallagher JT, Harding M, Dale RE. Sialic acid as a cell surface binding site for wheat germ agglutinin. In: Bog-Hansen TC, Spengler GA, eds. *The lectins: biology, biochemistry, clinical biochemistry*. Berlin and New York: Walter de Gruyter, 1983; 3: 311-8.
- 23 Gallagher JT, Morris A, Dexter TM. Identification of two binding site for wheat germ agglutinin on polylectosamine-type oligosaccharides. *Biochem J* 1985; 231: 115-22.
- 24 Cummings RD, Kornfeld S. Characterisation of the structural determinants required for the high affinity interactions of asparagine-linked oligosaccharides with immobilised *Phaseolus vulgaris* leucoagglutinating and erythroagglutinating lectins. *J Biol Chem* 1982; 257: 11230-4.
- 25 Stoddart RW, Roberts ISD. Interaction between mast cells and fibroblasts in neurofibroma: a commentary. *Pathol Res Pract* 1988; 183: 459-61.
- 26 Roberts ISD, Jones CJP, Stoddart RW. Lectin histochemistry of the mast cell: heterogeneity of rodent and human mast cell populations. *Histochem J* 1990; 22: 73-80.
- 27 Yamashita AK, Nitoi A, Kobata A. Structural determinants of *Phaseolus vulgaris* erythroagglutinating lectin for oligosaccharides. *J Biol Chem* 1983; 258: 14753-5.
- 28 Gipson IK, Riddle C, Kiorpes T, Spurr S. Lectin binding to cell surfaces: comparisons between normal and migrating corneal epithelium. *Dev Biol* 1983; 96: 337-45.
- 29 Bausch JN, Poretz RD. Purification and properties of the haemagglutinin from *Machra pomifera* seeds. *Biochemistry* 1977; 16: 5790-4.
- 30 Kefalides NA, Alper R, Clark CC. Biochemistry of basement membranes. *Int Rev Cytol* 1979; 61: 167.
- 31 Bishop PN, Jones CJP, Stoddart RW. An abnormal saccharide distribution in lattice corneal dystrophy. *J Pathol* 1989; 157: 166A (abstract).
- 32 McPherson S, Kiffney GT, Freed CC. Corneal amyloidosis. *Am J Ophthalmol* 1966; 62: 1025-33.
- 33 Dubord P, Krachmer J. Diagnosis in early lattice corneal dystrophy. *Arch Ophthalmol* 1982; 100: 788.
- 34 Garner A. Amyloidosis of the cornea. *Br J Ophthalmol* 1969; 53: 73-81.
- 35 Stern GA, Knapp A, Hood CI. Corneal amyloidosis associated with keratoconus. *Ophthalmology* 1988; 95: 52-5.
- 36 Folberg R, Alfonso E, Croxatto JO et al. Clinically atypical granular corneal dystrophy with pathologic features of lattice-like amyloid deposits. *Ophthalmology* 1988; 95: 46-51.

Audit of an ophthalmology waiting list

H F Thomas, R H J Darvell

Abstract

The hospital case notes of 209 (98%) of the 213 patients placed on an adult ophthalmic surgical waiting list between mid 1984 and mid 1985 were reviewed. Information on referral sources, previous eye surgery, outpatient visits, and treatment up to the end of 1987 was recorded. The vital status of patients up to the end of 1988 was also ascertained. Waiting list patients (123 women, 86 men) were elderly (73% over 65 years) and most (70%) were listed for cataract surgery. By the end of 1987 (30-42 months after waiting list entry) 64% of all patients (and 56% of cataract patients) had received surgery under the care of the health authority. The remainder had either died (12%), received surgery elsewhere (7%), were still on the waiting list (7%), no longer wanted or were unfit for surgery (6%), or had left the district (4%). By the end of 1988 (42-54 months after waiting list entry) 28% of the original waiting list population had died.

Medical audit has been defined as the systematic review by doctors of their own work¹ and as the detailed retrospective review and evaluation of selected medical records by qualified professional staff.² The present government has a commitment to establish medical audit in British hospitals,³ and the College of Ophthalmologists and the Royal College of Surgeons support this objective. This study is an attempt to audit an ophthalmic waiting list by examining background information about adult patients on a waiting list, some of the processes related to being placed on the list, outcome in terms of receiving surgery, and total mortality up to 54 months after being placed on the list. The study was also intended to provide some practical lessons in undertaking audit.

Materials and methods

The hospital case notes of 209 (98%) adults placed on the Thanet ophthalmic waiting list between 30 June 1984 and 31 July 1985 were reviewed and a number of facts abstracted and tabulated. Four sets of notes were not located. A list of patients with their dates of birth was sent to the local Registrar of Births and Deaths, and this department identified patients deceased locally up to the end of 1988.

Results

Table 1 shows the age and sex structure of the waiting list. Patients were mainly women (59%) and elderly, with 73% over 65 years and 47% over 75 years. Five patients were placed on the list twice for different procedures during the study period.

Table 2 shows the operations specified for waiting list patients. Cataract surgery was the commonest procedure (70%), with lacrimal, lid and glaucoma surgery together accounting for only 34 (17%) procedures.

SOURCES OF REFERRAL

Information on the sources of referral for the condition leading to entry on the waiting list was available for 189 (90%) patients. Most patients (92) had only been seen by their general practitioner, while 79 were referred by their general practitioner following a visit to an optician. Internal hospital referrals from diabetic and other clinics provided 18 patients.

PREVIOUS OPHTHALMIC TREATMENT

Review of previous ophthalmic notes showed that 32 (15%) patients had first seen local hospital ophthalmologists 10 or more years before the present study period (1984-5), and 75 (36%) had been first seen five or more years before entry to the waiting list. Eighty seven patients (42%) had received previous ophthalmic surgery in the district for conditions such as cataract (39), glaucoma (10), lacrimal problems (8), squint (6), and retinal detachment (5). Thirty-two (22%) of the cataract operations specified on the waiting list were to second eyes.

OUTPATIENT VISITS BEFORE WAITING LIST ENTRY

Table 3 shows the number of outpatient visits people made before being placed on the waiting list. About a fifth of patients (22%) were entered on their first visit, half were listed within five visits, while a quarter (28%) made 10 or more visits before going on the list.

Table 1 Age and sex of waiting list patients

Sex	Age group (years)					All ages
	15-44	45-64	65-74	75-84	85+	
Male	11	18	28	24	5	86
Female	4	24	25	61	9	123
Total	15	42	53	85	14	209

Five patients are included twice (see text).

Table 2 Operations specified for 209 waiting list patients

Operation	Number	Percentage
Cataract extraction	147	70
Lacrimal surgery	18	9
Lid surgery	8	4
Glaucoma surgery	8	4
Squint surgery	7	3
Retinal surgery	5	2
Skin grafting	4	2
Pterygium removal	3	1
Vitrectomy	2	1
Other procedures	7	3

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OUTCOME FOR WAITING LIST PATIENTS

Table 4 shows what had happened to patients by the end of 1987 (30–42 months from waiting list entry). Overall 133 (64%) patients had received surgery in the district eye unit, with a lower percentage (82:56%) of cataract patients being treated at the unit. For the 82 patients who received cataract surgery the waiting times after being placed on the list were less than a year for 22 (27%), between one and two years for 14 (17%), and between two and three years for 46 (56%). Fourteen other cataract patients had surgery elsewhere either privately (9), at Moorfields (4), or in another district (1).

Patients did not receive surgery for a variety of reasons, the main one (12%) being death before being called for surgery. Of the 27 patients who died while on the waiting list during the 42-month follow-up period, seven died within the first year, 15 after one to two years, and five after two years. Review of local death registers up to the end of 1988 (42–54 months from waiting list entry) identified 58 deaths (28%) in the study population. None was linked to operative complications. The deceased were elderly on entry to the waiting list (mean age: males 77 years, females 78 years), and deaths were equally distributed among the sexes (28% males, 29% females).

Thirty-six (27%) of the 133 patients who received surgery under the district health authority had their operation postponed once (29), twice (4), and even three times (3). Hospital factors, such as no anaesthetist or no bed accounted for 17 postponements, with patient factors, such as ill health, contributing to the remainder. The case notes of patients were reviewed mainly during the first half of 1988, by which time 34 (17%) of the study population had either been listed for or undergone further ophthalmic surgery in the district.

Table 3 Number of outpatient visits before being placed on waiting list

Number of visits	Number of patients	Percentage	Cumulative % (rounded up)
1	44	21.7	22
2	16	7.9	30
3	18	8.9	39
4	8	3.9	42
5	16	7.9	50
6	17	8.4	59
7	11	5.4	64
8	9	4.4	69
9	9	4.4	73
10	3	1.5	74
11–14	13	6.4	81
15–19	9	4.4	85
20–24	12	5.9	91
25–30	3	1.5	93
31+	15	7.4	100

n=203 (information not available for six patients).

Table 4 Outcome for waiting list patients up to the end of 1987

Outcome	All patients (n=209)		Cataract patients (n=147)	
	Number	Percentage	Number	Percentage
Operations under health authority care	133	64	82	56
Died before surgery	26	12	24	16
Surgery elsewhere	15	7	14	10
Still on waiting list	14	7	13	9
No longer wanted surgery or unfit for surgery	13	6	10	7
Left district	8	4	4	3

Discussion

This project was made possible because a medical records officer kept a complete record of adult patients entered in a waiting list over the previous four years. The waiting lists for children, minor operations, and laser treatment were incomplete for the study period, and these patients were therefore excluded from the study. In many districts waiting lists are kept as a card index and cannot be reconstructed for past years, thus making this type of study impossible.

Obtaining the patients' case notes was hindered by staffing shortages in the medical records department, a not uncommon situation in many British hospitals. The District Department of Public Health Medicine provided clerical help to obtain medical records and to process the data. Reviewing hospital notes and searching for entries relevant to a single specialty is time consuming even when carried out by medical or nursing staff. It took between 3 and 20 minutes to review and abstract information from individual case notes.

The age of the waiting list population reflects the high proportion of elderly people resident in the district (22% over 65 years compared with 15% in England and Wales). General practitioners rather than opticians appear to be the main source of outpatient referrals, a finding consistent with those of other studies.⁴ Almost half (42%) of the waiting list group had previously undergone ophthalmic surgery and at least 17% of the group were listed to receive or had received further eye surgery after the operation specified in the study period. This illustrates the continuing demand for eye surgery by old as well as new patients.

Only a small proportion of eye patients are discharged from eye clinics, and most, particularly those with glaucoma or retinal problems, are kept under long term outpatient review. This maintains constant pressure on outpatient departments. Most of the case notes reviewed recorded at least one 'clinics cut down' when patients' appointments had had to be postponed to accommodate more urgent cases. Long term follow-up makes it difficult to isolate separate medical episodes when reviewing notes. The criterion for new cases was a new general practitioner's letter or casualty attendance. General practitioners' letters seeking to expedite treatment for patients already under follow-up were excluded. Most of the patients who made more than 10 outpatient visits before entry to the waiting list had been on long term medical treatment, for example for glaucoma, or had received surgery to one eye and were being followed up to ensure that their second eye received appropriate treatment, for example for cataract. Cataract surgery on the second eye (that is, one eye already having undergone cataract removal) is standard policy in the district despite the heavy workload. We understand that in some districts few second eyes are done in elderly patients. This may keep waiting lists down but does not perhaps offer the optimum standard of care.

The finding that only two-thirds of all waiting list patients and only just over half of the cataract patients reach surgery under district health

authority care is disappointing. Surgical operation rates compare favourably with those of other districts, but the present surgeons inherited long waiting lists, and the aging population has meant that demand for eye surgery has continued to grow. To tackle the long waiting list an Operation Cataract scheme was undertaken in 1989.⁵ Other measures to reduce surgical waiting times are also being taken. Official statistics⁶ for 1988 show that 36% of the district's ophthalmic patients were waiting over 12 months for surgery. The Operation Cataract scheme has improved this situation, and average waiting times are now about six to nine months. In England and Wales 17% of the 66 000 patients waiting for ophthalmic surgery had waited for over one year since entry to the waiting list.⁶ A quarter of health districts in England and Wales offering ophthalmic surgery have a higher proportion of patients waiting over 12 months for eye surgery than in Canterbury and Thanet. The situation in our authority is therefore not uncommon. This delay to surgery is regrettable in view of the benefits that surgery can bring and also the limited life expectancy of the elderly patients. Over a quarter of the study

population were dead within four years of going on the waiting list. This figure may be an underestimate, as only local death records were searched, and some patients may have moved away and died.

This study, by examining a defined population prospectively, gives a better insight into the dynamics of a waiting list than does the review of cross-sectional routine statistics which do not follow up the fate of individual patients.

We gratefully acknowledge the help of medical records officers, Thanet District General Hospital, Mr Newman, Registrar of Births and Deaths, Thanet District, Professor L Opit, Centre for Health Service Studies, University of Kent, and Mr I Dawson, who provided computing assistance.

- 1 Shaw CD. Acceptability of audit. *Br Med J* 1980; 281: 1443-5.
- 2 Rogers PG. *Discursive dictionary of health care* - subcommittee on health and environment. Washington: US Government Printing Office, 1976.
- 3 Department of Health Working Party No 6. *Medical audit*. London: HMSO, 1989.
- 4 Harrison RJ, Wild JM, Hobley AJ. Referral patterns to an ophthalmic outpatient clinic by general practitioners and ophthalmic opticians and the role of these professionals in screening for ocular disease. *Br Med J* 1988; 297: 1162-7.
- 5 Thomas HF, Darvell RHJ, Hicks C. 'Operation cataract', a means of reducing waiting lists for cataract operations. *Br Med J* 1989; 299: 961-3.
- 6 College of Health. *Guide to hospital waiting lists*. London: College of Health, 1989.

FIFTY YEARS AGO

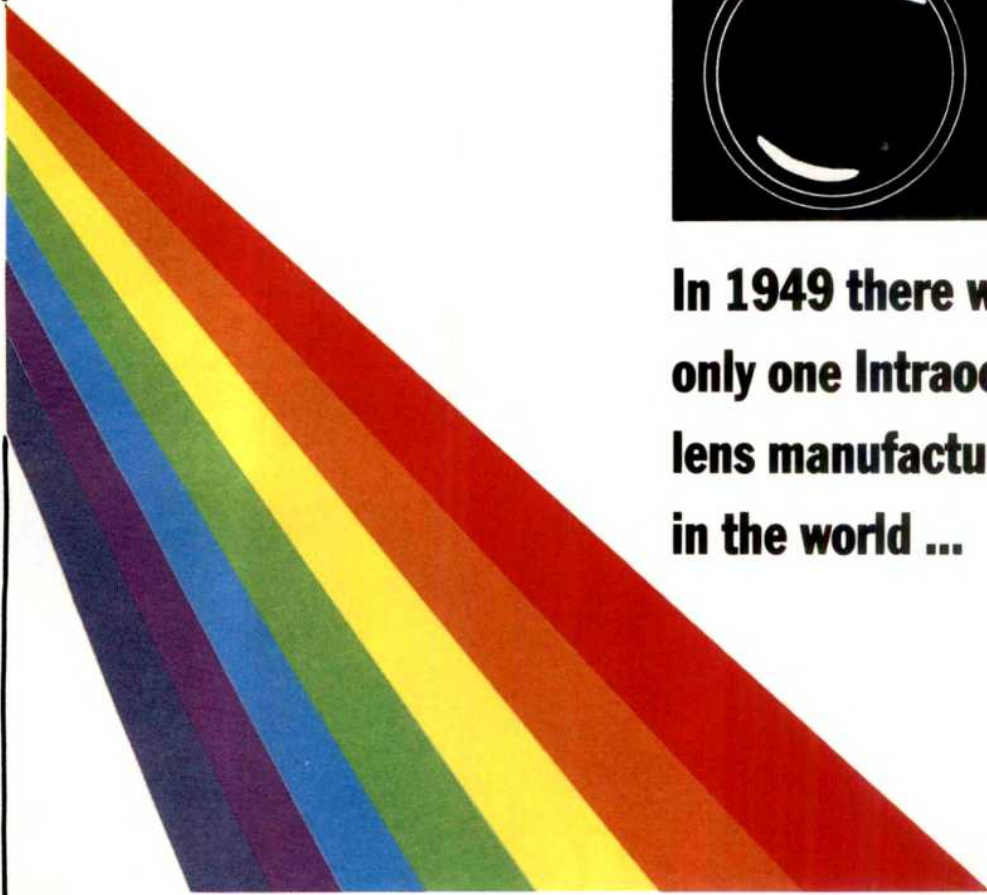
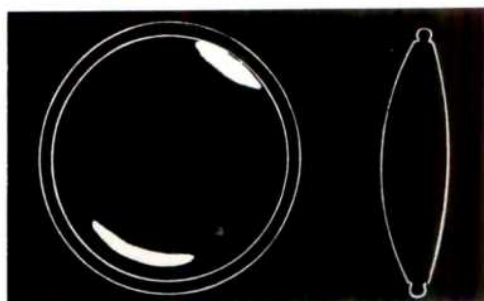
Annotation: 'My eyes are dim'

The fact that one of the marching songs of the British army in the current war begins 'My eyes are dim, I cannot see,' is of interest as we believe it to be the first instance of an ophthalmic sentiment being made use of in this connexion. In the Great War 'Tipperary' held the field; in the present 'Roll out the barrel' bids fair to be as popular. The Marseillaise must, we think, be the most famous marching song in history, though 'John Brown's body' runs it close. The fact that Uncle Toby was addicted to whistling half-a-dozen bars of 'Lillibullero' leads one to the conclusion that those British soldiers, who swore so terribly in Flanders, got rid of some of their superfluous energy with this tune. The French are said to have used 'Malbrouk s'en va-t-en guerre' during the Revolution. Brewer, in his Dictionary of Phrase and Fable, says that this song dates from the Crusades and has nothing to do

with the Duke of Marlborough; and it is now chiefly memorable for Thackeray's ridiculous drawing of Duchess Sarah taking leave of her husband. Was Kipling's 'Absent minded beggar' much used in the South African war of 1899-1902? Our Scottish readers, if any chance upon this note, will doubtless hum 'Hey Johnny Cope'; and it is common knowledge that Cromwell's Ironsides went into action singing psalms. Napoleon gave orders that French troops in the Peninsula should be supplied with at least three different songs, and for all we know to the contrary William the Conqueror may have countenanced a marching song at Hastings. Marching songs are probably as old as armies themselves.

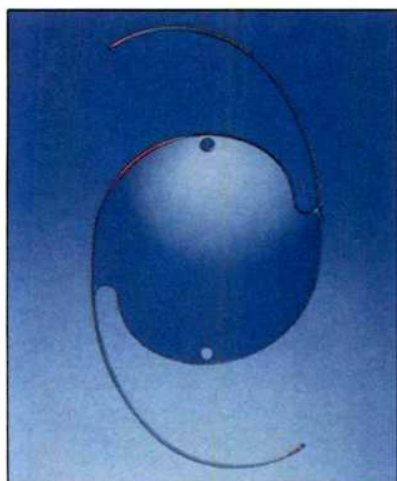
We have even heard of an example of ophthalmic humour in the eye ward of one of the London Hospitals where the children greeted the dawn with the roundelay 'Dancing with tears in my eyes.'

Br J Ophthalmol 1940; 24: 360.



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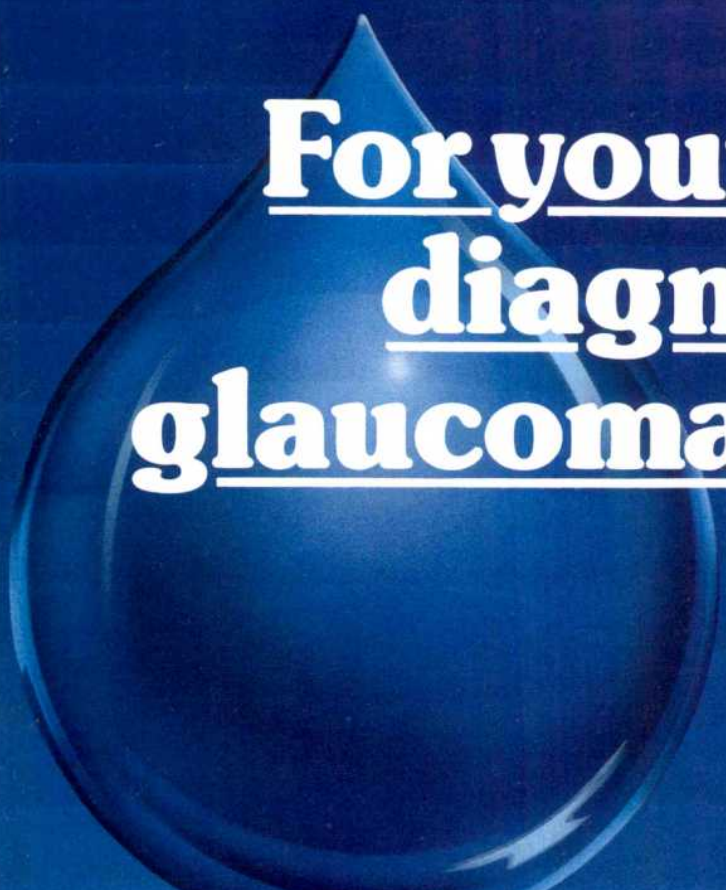


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References

1. Maclure, G.M. et al. 3rd Congress of European Glaucoma Society, 1988.
2. Kitazawa, Y. et al. Acta XXIV International Congress of Ophthalmology, 1983. P. Henkind (Ed), Lippincott, Philadelphia.
3. Hugues, F.C. et al. J. Fr. Ophthalmol. 1987; **10**, 8/9, 485-490.
4. Negishi, C. Acta Soc. Ophthalmol. Jpn. 1982; **85**, 57-66.
5. Scoville, B. et al. American Journal of Ophthalmology, 1988; **105**, No.2, 150-154.

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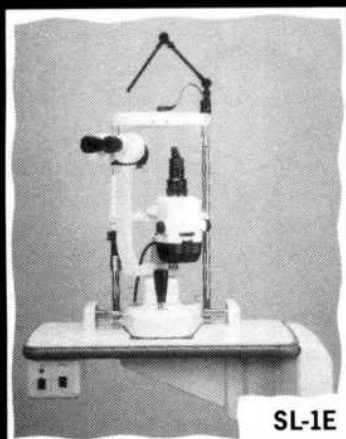
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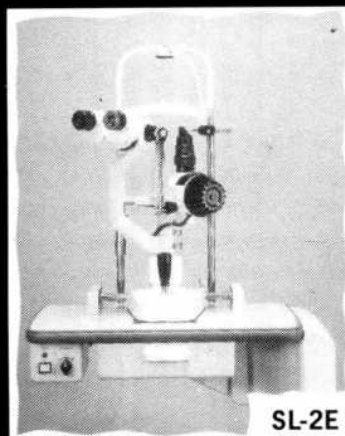
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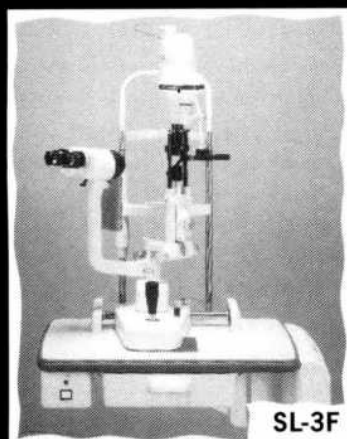
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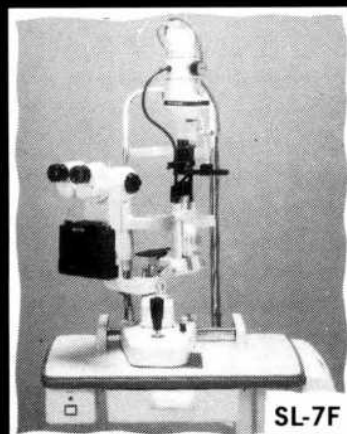
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Anisocoria in unilateral ophthalmic disease

Russell V Pearson, Geoffrey E Rose

Abstract

Pupillary diameters in the affected and unaffected eyes of 327 patients with unocular red eye were assessed during fixation of a distant target. The mean pupillary diameters were similar in the unaffected eyes in each of eight diagnostic groups, but were significantly different ($F=3.84$, $p<0.001$) in the diseased eyes. With corneal abrasions ($p<0.001$), marginal keratitis ($p<0.05$), and acute anterior uveitis ($p<0.001$) the mean pupillary diameter for the affected eye was significantly smaller than that of the unaffected eye. The observed differences of pupillary diameter probably reflect the role of neuronal and autocoid mechanisms in the unilateral control of pupillary size.

The ocular response to injury comprises a reduction in the blood-ocular barrier, an intraocular pressure rise, and miosis.¹⁻⁴ It is probable that the changes in the blood-ocular barrier and intraocular pressure are due to concentration of prostaglandins within the eye,²⁻⁴ this being a result of both increased production within^{4,5} and decreased clearance from⁶⁻⁸ the eye. The miosis, however, is probably caused both by intracamerally acting prostaglandin accumulation and by substance P acting on the smooth muscle of the sphincter pupillae, this neuropeptide being released from trigeminal sensory radicals within the iris.⁹⁻¹¹ The stimulus for the release of substance P is probably depolarisation of afferent sensory trigeminal fibres in the cornea and other ocular structures, with the efferent path being mediated through an axonal reflex.¹² Central or peripheral trigeminal denervation reduces the accumulation of substance P and the miosis in response to injury.¹⁰ Calcitonin gene-related peptide (CGRP) occurs within trigeminal nerve fibres¹³⁻¹⁵ and dilates ocular blood vessels. CGRP and substance P might act synergistically in mediation of the ocular response to injury.^{16,17}

Miosis within an inflamed eye, as compared to the unaffected fellow eye, is generally recognised among ophthalmologists as frequently being a sign of significant ocular pathology. The actual incidence in various diseases would not, however, appear to have been recorded.

In the present report the changes of pupillary diameter are determined for various diseases causing unocular red eye, and the changes are considered in relation to the neuronal and autocoid mechanisms affecting pupillary diameter in a single eye.

Patients and methods

The pupillary diameter of patients with unilateral red eye, attending the Accident and Emergency Department of Moorfields Eye Hospital, was

assessed in a room with uniform illumination of moderate intensity (approximately 1000 lux). The patient was instructed to fixate a distant, non-accommodative target at 3 metres, and the pupillary diameters were assessed by matching with a comparative scale. The scale was held alongside the pupil, care being taken to avoid the visual axis of the patient. The scale had 'half-pupil' marks along one edge, with diameter increments of 1 mm, thereby permitting diameter estimates to 0.5 mm gradations.

After recording the assessment of pupil size, a problem orientated history and ophthalmic examination was performed. The iris colour was also recorded.

Results

Three hundred and twenty-seven patients (213 male, 114 female) were enrolled in the study. In 317 patients the condition was one of eight major diagnostic categories (Table 1), and others (6 male, 4 female) having various conditions, namely trauma (5 eyes), stromal keratitis (2 eyes), corneal abscess (1 eye), chemical injury (1 eye), and acute angle-closure glaucoma (1 eye).

There was a predominance of males over females in all diagnostic groups except episcleritis (with a similar sex incidence). Dendritic keratitis and corneal foreign bodies occurred almost exclusively in men (Table 1).

There was a significant difference between the mean ages at presentation (Table 1. One-way analysis of variance: $F_{7,309}=4.92$, $p<0.001$). Patients with subconjunctival haemorrhage were significantly older than those in each of the other seven diagnostic groups – that is, marginal or dendritic keratitis ($p<0.05$), corneal foreign body, episcleritis or iritis ($p<0.01$), and conjunctivitis or corneal abrasion ($p<0.001$). Similarly, those patients with marginal keratitis were significantly older than those with conjunctivitis ($p<0.01$) or corneal abrasion ($p<0.05$), and those with iritis were significantly older than those with conjunctivitis ($p<0.05$).

In the group overall, the side of involvement was similar (162 right, 155 left), though there was some variability between the subgroups. Likewise, with the exception of episcleritis, the ratio of involvement of blue/grey eyes with respect to brown/green was similar in all the groups (Table 1).

The average pupillary diameters in the unaffected 'white' eyes in the eight categories were not significantly different (Table 2, $F_{7,309}=1.57$). In contrast, for the 'red' eyes there were significant differences between the mean diameters for the various diagnoses $F_{7,309}=3.84$, $p<0.001$. The mean pupillary diameter for eyes with conjunctivitis (4.27 mm, 131 eyes) and iritis (3.65 mm, 44 eyes) were significantly ($p<0.001$) different, as were the diameters for eyes with

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Table 1 Characteristics and diagnosis for 317 patients with unilateral ophthalmic disease

Diagnosis	Number of patients	Sex ratio (male/female)	Age (yr) mean (SD) (range)	Inflamed eye (right/left)	Iris colour (blue/brown)
Subconjunctival haemorrhage	23	16/7 (2.29)	53.6 (17.9) (19-84)	10/13	15/8 (1.88)
Conjunctivitis	131	75/56 (1.34)	36.3 (14.7) (9-70)	70/61	83/48 (1.73)
Episcleritis	13	6/7 (0.86)	37.6 (13.7) (23-67)	6/7	5/8 (0.62)
Corneal foreign body	16	15/1 (15.0)	38.8 (10.3) (23-59)	5/11	10/6 (1.67)
Corneal abrasion	51	35/16 (2.19)	37.0 (11.5) (16-62)	25/26	34/17 (2.00)
Marginal keratitis	31	21/10 (2.10)	44.4 (14.5) (19-69)	20/11	19/12 (1.58)
Dendritic keratitis	8	8/0 (-)	36.8 (16.3) (20-60)	1/7	5/3 (1.67)
Acute Anterior uveitis	44	31/13 (2.38)	41.8 (16.8) (19-79)	25/19	29/15 (1.94)
Totals	317	207/110 (1.88)	(39.4 yr) (9-84)	162/155	200/117 (1.71)

Table 2 Estimates of pupillary diameters in each of eight diagnostic categories of patients with unilaterally inflamed ('red') eye

Diagnosis	Number of patients	Pupil diameter* of:		Difference* (mm) ('white'-'red')
		'white' eye	'red' eye	
Subconjunctival haemorrhage	23	3.89 (0.64)	3.96 (0.67)	-0.065 (0.23) $t=1.36, p>0.1$
Conjunctivitis	131	4.31 (1.00)	4.27 (0.48)	+0.042 (0.26) $t=1.84, p>0.05$
Episcleritis	13	3.77 (1.11)	3.77 (1.11)	(-)
Corneal foreign body	16	3.75 (0.97)	3.63 (0.92)	+0.125 (0.34) $t=1.47, p>0.1$
Corneal abrasion	51	4.08 (1.14)	3.74 (1.05)	+0.343 (0.51) $t=4.80, p<0.001$
Marginal keratitis	31	4.10 (1.29)	3.89 (1.22)	+0.210 (0.51) $t=2.29, p<0.05$
Dendritic keratitis	8	3.75 (0.76)	3.25 (0.89)	+0.500 (0.66) $t=2.14, p>0.05$
Acute anterior uveitis	44	4.10 (0.87)	3.65 (0.84)	+0.455 (0.62) $t=4.87, p<0.001$

* Mean (standard deviation).

Table 3 The incidence of anisocoria in each diagnosis and the frequency of anisocoria in which the pupil is smaller on the affected ('red') side

Diagnosis	Number(%) of patients with anisocoria (blue/brown)	Number with red eye smaller anisocoria			Significance (p)*
		All eyes†	Blue eyes	Brown eyes	
Subconjunctival haemorrhage	2 (9%) (1/1)	0/2	0	0	0.48
Conjunctivitis	14 (11%) (7/7)	11/14	6	5	0.06
Episcleritis	0 (0%)	0	0	0	-
Corneal foreign body	5 (31%) (3/2)	4/5	3	1	0.37
Corneal abrasion	21 (41%) (14/7)	20/21	13	7	<0.0001
Marginal keratitis	10 (32%) (7/3)	9/10	6	3	<0.03
Dendritic keratitis	4 (50%) (3/1)	4/4	3	1	0.13
Acute anterior uveitis	24 (55%) (20/4)	22/24	19	3	<0.0002

* Two-tail probability of drawing observed overall incidence (†) of 'red eye smaller' anisocoria.

subconjunctival haemorrhage (3.96 mm, 23 eyes) and dendritic keratitis (3.25 mm, 8 eyes; $p<0.05$).

The difference between fellow eyes ('white' eye pupillary diameter minus 'red' eye pupillary diameter) is presented in Table 2. Average differences were significantly different from zero in the groups with marginal keratitis ($p<0.05$), corneal abrasion ($p<0.001$), or iritis ($p<0.001$).

The incidence of anisocoria varied with the different diagnoses—between 0% with episcleritis and 55% with uveitis (Table 3). The relative

frequency of anisocoria in blue/grey eyes as compared with brown/green eyes with the same diagnosis ranged from 1.0 for subconjunctival haemorrhage or conjunctivitis to 5.0 for iritis (Table 3). This contrasts with an iris colour frequency-ratio of 1.71 for blue/grey eyes with respect to brown/green eyes.

In the 80 eyes with anisocoria, 'red eye smaller' anisocoria occurred in 70 eyes, and the proportion was similar in the two groups of iris colouration (for each of the diagnoses—Table 3). The incidence of 'red eye smaller' anisocoria, without respect to iris colour, ranged from 0% (with subconjunctival haemorrhage) to greater than 90% (marginal keratitis, iritis, corneal abrasion, or dendritic ulceration). The probability of drawing the incidences as observed, or ones more extreme, is presented in Table 3. In each of the three conditions with significant anisocoria the symptoms were of similar duration in those eyes with and those without unequal pupils. With marginal keratitis the mean duration of symptoms in the anisocoric group was 4.6 days (SD 8.3 days, 10 eyes), whereas those with equal pupils had 3.9 days' mean duration (SD 3.1 days, 21 eyes), and, similarly, with corneal abrasion (anisocoric: 2.6, SD 4.4 days, 21 eyes; isocoric: 2.3, SD 3.2, days, 30 eyes) and with iritis (anisocoric: 5.0, SD 7.2, days, 24 eyes; isocoric: 9.8, SD 15.6, 20 eyes).

Discussion

In the present investigation a relative miosis, significant in both degree and incidence, was present in eyes with corneal abrasion, marginal keratitis, and acute anterior uveitis. This possibly reflects the mechanisms involved in the ocular response to injury.

Corneal abrasion is associated with marked stimulation of afferent fibres of the trigeminal nerve; manifest clinically as extreme pain. In these eyes it is probable that the miosis is mediated through a trigeminal axon reflex, with release of substance P (and possibly CGRP) at nerve fibres on the sphincter pupillae.

With acute anterior uveitis the miosis is probably due to an accumulation of prostaglandins and other autoids within the inflamed eye.¹⁷⁻¹⁹ The presence of pain with acute anterior uveitis might, however, imply a partial mediation through trigeminal axon reflexes. Similarly, the miosis of marginal keratitis is probably induced by both neuronal and autoid mechanisms, marginal keratitis being an immune process occurring at a site rich in trigeminal sensory innervation.

Subconjunctival haemorrhage, conjunctivitis, and episcleritis did not cause a significant miosis in the present investigation, perhaps because these diseases occur in tissues remote from the anterior chamber of the eye and in tissues with relatively poor trigeminal innervation.

The absence of significant miosis with corneal foreign bodies or dendritic keratitis (Tables 2 and 3) would appear to be enigmatic, these lesions arising in tissues with considerable trigeminal innervation. However, although a corneal foreign body disrupts corneal (trigeminal) nerves, this occurs over a very much

smaller area than that with most corneal abrasions. Moreover, whereas an abrasion exposes nerve endings, those under a foreign body are not exposed to the external environment. The relatively painless nature of corneal foreign bodies, as compared with abrasions, is compatible with a reduced trigeminal afferent stimulation. The lack of a significant miosis with herpetic dendritic keratitis is probably due to insufficient numbers in this group (eight cases). It is possible, however, that both the absence of intraocular inflammation and a malfunctioning of virus affected trigeminal neurons might reduce the incidence of miosis in such eyes.

To elucidate further the mechanisms causing miosis in ocular disease it would be of particular interest to ascertain whether blockage of the trigeminal afferent response with topical anaesthesia reduces or prevents the miosis in, for example, patients with corneal abrasion. Similarly, the use of antagonists to prostaglandin synthesis might prevent the miosis associated with marginal keratitis or acute anterior uveitis, this reflecting a role for autocoids in these diseases.

- 1 Podos SM. Prostaglandins, non-steroidal anti-inflammatory agents and eye disease. *Trans Am Ophthalmol Soc* 1976; 74: 637-60.
- 2 Hall DWR, Bonta IL. Prostaglandins and ocular inflammation. *Doc Ophthalmol* 1977; 44: 435-44.
- 3 Bhattacharjee P. Prostaglandins and inflammatory reactions in the eye. *Methods Find Exp Clin Pharmacol* 1980; 2: 17-31.
- 4 Eakins KE. Prostaglandin and non-prostaglandin breakdown of the blood-aqueous barrier. *Exp Eye Res* 1977; 25 (suppl): 483-98.
- 5 Bhattacharjee P, Eakins KE. Inhibition of the prostaglandin synthetase systems in ocular tissues by indomethacin. *Br J Ophthalmol* 1974; 50: 227-30.
- 6 Bitó LZ, Salvador EV. Intraocular fluid dynamics. III. The site and mechanism of prostaglandin transfer across the blood-intraocular fluid barriers. *Exp Eye Res* 1972; 14: 233-41.
- 7 Bitó LZ. The effects of experimental uveitis on anterior uveal prostaglandin transport and aqueous humor composition. *Invest Ophthalmol Vis Sci* 1974; 13: 959-65.
- 8 Bitó LZ, Wallenstein MC. Transport of prostaglandins across the blood-brain and blood-aqueous barriers and the physiological significance of these absorptive transport processes. *Exp Eye Res* 1977; 25 (suppl): 229-43.
- 9 Bill A, Stjernschantz J, Mandall A, Brodin E, Nilsson G. Substance P: release on trigeminal nerve stimulation and effects on the eye. *Acta Physiol Scand* 1979; 106: 371-3.
- 10 Butler JM, Powell D, Unger WG. Substance P levels in normal and sensorily denervated rabbit eyes. *Exp Eye Res* 1980; 30: 311-3.
- 11 Stjernschantz J, Sears M. Involvement of substance P in the antidromic vasodilation and barrier disruption of the rabbit eye. *Invest Ophthalmol Vis Sci (ARVO suppl)* 1982; 22: 180.
- 12 Butler JM, Unger WG, Cole DF. Axon reflex in ocular injury: sensory mediation of the response of the rabbit eye to laser irradiation of the iris. *Q J Exp Physiol* 1980; 65: 261-72.
- 13 Terenghi G, Polak JM, Ghatel MA, et al. Distribution and origin of calcitonin gene-related peptide (CGRP) immunoreactivity in the sensory innervation of the mammalian eye. *J Comp Neurol* 1985; 233: 506-15.
- 14 Stone RA, Kuwayama Y, Terenghi G, Polak JM. Calcitonin gene-related peptide: occurrence in corneal sensory nerves. *Exp Eye Res* 1986; 43: 279-90.
- 15 Stone RA, McGlinn AM. Calcitonin gene-related peptide immunoreactive nerves in human and rhesus monkey eyes. *Invest Ophthalmol Vis Sci* 1988; 29: 305-10.
- 16 Wahlstedt C, Beding B, Ekman R, Oksala O, Stjernschantz J, Hakanson R. Calcitonin gene-related peptide in the eye: release by sensory nerve stimulation and effects associated with neurogenic inflammation. *Regul Pept* 1986; 16: 107-15.
- 17 Unger WG, Terenghi G, Ghatel MA, et al. Calcitonin gene-related polypeptide as a mediator of neurogenic ocular injury response. *J Ocul Pharmacol* 1985; 1: 189-99.
- 18 Bhattacharjee P. Release of prostaglandin-like substances by shigella endotoxin and its inhibition by non-steroidal anti-inflammatory compounds. *Br J Pharmacol* 1975; 54: 489-94.
- 19 Eakins KE, Whitelocke RAF, Bennett A, Martenet AC. Prostaglandin-like activity in ocular inflammation. *Br Med J* 1972; ii: 452-3.

Long-term efficacy of primary laser trabeculoplasty

T. Elsäas, H. Johnsen

Abstract

Sixty glaucomatous eyes of 60 patients treated with laser trabeculoplasty as primary therapy were reviewed retrospectively. There were 42 eyes with capsular glaucoma and 18 with simple glaucoma. The mean pre-laser intraocular pressure (IOP) was 35.2 (SD=6.5) mmHg. Success was defined as IOP $\leq$ 22 mmHg without medication. The probability of success was 0.73 at 1 year, 0.66 at 2 years, 0.57 at 3 years, and 0.50 at 4 years. Three eyes experienced progressive visual field loss or disc damage in spite of an intraocular pressure below 22 mmHg without medication. High pre-laser pressure and the severity of the visual field defects were significant predictors of treatment failure.

Laser trabeculoplasty (LTP) was introduced as an alternative to filtering surgery in the pre-surgical glaucoma patient on full medication.¹ Several reports have noted the efficacy and low complication rate associated with this procedure.¹⁻³ There are now a number of studies of it as a primary treatment in glaucoma.⁴⁻⁹ The first results of a multicentre controlled study have recently been published.¹⁰ To the best of our knowledge there are only two reports on long term results with primary LTP.¹¹

We have retrospectively studied the long term results with laser as primary treatment in 60 eyes of 60 patients.

Material and methods

The patients were collected from two earlier prospective studies on primary LTP investigating 180° versus 360° treatment¹¹ and the immediate pressure response to one- and two-stage LTP.¹² In these two studies 66 eyes were treated in 60 patients. For six patients one eye was randomised for one-stage and the other for two-stage treatment. One eye from each of these patients was randomised to the present study. There were 25 women and 35 men in the study sample. The mean age was 71.5 (SD=9.2) years. The material consisted of 18 eyes with simple glaucoma and 42 with capsular glaucoma.

The patients had to meet all of the following criteria to be included in the original two studies: (a) IOP $\geq$ 25 mmHg on each reading of the pre-laser diurnal curve; the mean of these measurements was taken as pre-laser IOP; (b) glaucomatous disc damage and/or visual field defects; (c) no earlier glaucoma treatment.

The cupping and pallor of the disc were evaluated with a Goldmann contact lens according to Schwartz.¹³ Fundus photography was not performed. Glaucomatous damage of the optic nerve head was defined as a vertical cup-disc ratio $\geq$ 0.5 and at least one of the following

criteria: (a) cupping of the optic nerve head extending to the margin of the disc; (b) a difference of 0.2 or more of the C/D ratio between the two eyes; (c) different degrees of disc pallor in the two eyes with no other explanation subjectively assessed by one of the authors (TE) by contact lens examination.

Progressive disc damage was judged to have occurred with an increase in the C/D ratio of 0.2 or more and/or cupping progressing to the disc margin. Disc changes were subjectively estimated by one of the authors (TE) by contact lens examination comparing the present findings with the written description and drawings from the entry of the patients into the two earlier prospective LTP studies,^{11,12} using the recommendations of Schwartz.¹³ The optic nerve head was in these two studies evaluated by the same person (TE).

The visual field was examined with the Humphrey Visual Field Analyzer using the suprathreshold Armaly full field screening test¹¹ or the suprathreshold 76-point central screening test.¹² Both programs apply a quantified defect strategy. The original study¹¹ started some months before our automated perimetry service was established, and during this period the visual fields were plotted by Goldmann perimetry. In addition Goldmann perimetry was performed in patients who did not co-operate during automated perimetry or who had extensive central field defects. Glaucomatous visual field defects were defined as having at least three contiguous spots within the central 30° field and a depth of $\geq$ 5 dB. We used the criteria of Ticho and Nesher³ for detecting visual field decay in eyes monitored by automated perimetry and the criteria of Kidd and O'Connor¹⁴ in patients followed up by Goldmann perimetry. Visual field deterioration was confirmed by retesting. Visual field defects were given scores according to the following classification.

0: Normal.

1: Scattered defects with a depth of $\geq$ 5 dB not creating a complete Bjerrum scotoma.

2: Spots with a depth $\geq$ 5 dB creating a complete Bjerrum scotoma extending from the blind spot to the horizontal nasal meridian.

3: Larger defects than 2.

Goldmann defects were classified according to Aulhorn.¹⁵ The pigmentation of the chamber angle was not evaluated.

All patients were scheduled for re-examination by one of the authors and had the same ophthalmic examination as in the two reports^{11,12} which recruited the patients to our study. Four patients died during the observation period and one patient did not attend for examination. The files of these patients were checked for the information needed, and it was included in the material up to their last visit.

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Success was defined as IOP ≤ 22 mmHg without medication. When the patient did not meet those criteria the result was classified as failure. If the IOP exceeded 22 mmHg, topical medication was added. If this was not sufficient, the patient was referred for trabeculectomy. During the first two weeks after laser treatment higher pressure levels were allowed before starting medication. If the intraocular pressure was ≥ 40 mmHg the day after LTP, ≥ 30 mmHg after one week, or ≥ 25 mmHg after two weeks, medication was prescribed.

LTP was performed with a Coherent argon laser photocoagulator. The spots were placed just in front of the scleral spur, with blanching, bubble formation, and pigment dispersion as the criteria for adequate laser exposure. Application parameters were 50 μ m spot size, 0.1 second duration, and a mean power of 1.2 W (range 0.8–2.0). The treatment was performed by one of the authors to keep the technique unchanged during our two studies. One hundred spots were distributed in 360° except for 14 eyes randomised to two sessions of 50 spots in 180° with an interval of four weeks.

Since the purpose of the present work is to relate the outcome of primary LTP to elapsed time and certain characteristics of the subjects under study (age, type of glaucoma, pretreatment IOP, etc), lifetime data analysis (survival analysis) expressing the characteristics as concomitant variables in a regression model is appropriate.¹⁶

The probability of success (survivor function) is estimated by the Kaplan-Meier method.¹⁷ A hazard plot is shown to indicate the failure rate pattern, and the empirical failure rate is also estimated. The predictors of failure are evaluated by the Cox regression model¹⁸ using a stepwise procedure as implemented in the Survival module in the SYSTAT statistical package.¹⁹ Model control is carried out by residual analysis and graphical methods.

Results

Prelaser variables are listed in Table 1.

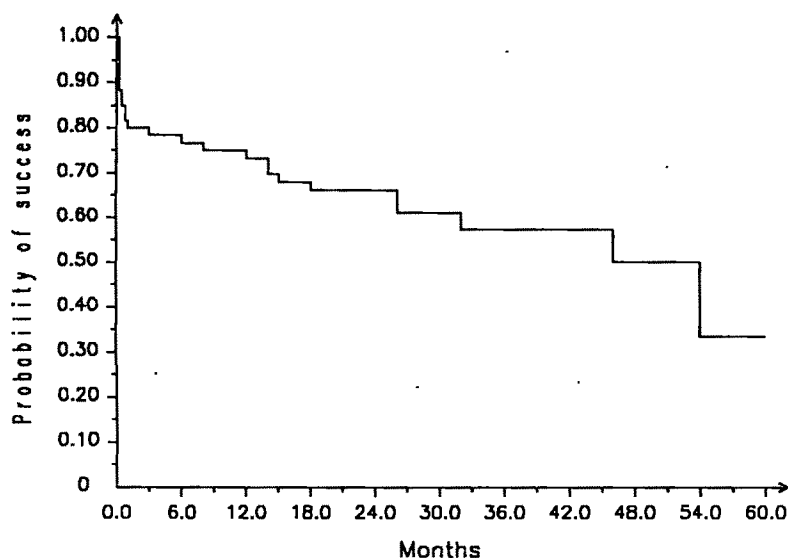


Figure 1 Kaplan-Meier plot showing probability of success for glaucomatous patients treated with primary LTP.

Table 1 Prelaser variables in eyes treated with primary LTP

Mean age	71.5 (SD=9.2) years
Mean prelaser IOP	35.2 (SD=6.5) mmHg
Mean cup-disc ratio	0.72 (SD=0.16)
Number of eyes (%) with cupping extending to the margin of the disc	26 (43%)
Mean visual field defects score in eyes examined with automated perimetry	1.5 (SD=1.4)

The total number of observations was 60, 23 of which were observed to fail. The Kaplan-Meier plot in Fig 1 shows the unconditional probability of success as a function of time since treatment. Accordingly, the probability of success was 0.73 at 1 year, 0.66 at 2 years, 0.57 at 3 years, and 0.50 at 4 years.

The hazard plot (Fig 2) indicates a rapidly decreasing failure rate during the first month after treatment, presumably because of failure in non-responders. The failure rate flattened out to a reasonably stable level, and increased towards the end of the observation period as seen in Fig 3. Twelve of a total of 23 failures occurred during the first month after LTP.

The high initial failure rate had a marked effect on the probability of success in the whole material. It is therefore worthwhile assessing the probability of success given success at 1 month. These probabilities were as follows: 0.92 at 1 year, 0.83 at 2 years, 0.72 at 3 years, and 0.63 at 4 years. Of the observed 23 eyes which failed, 18 needed medication on account of high pressure, and five were referred to trabeculectomy because of high IOP. Mean postlaser pressure in successfully treated eyes on the last visit was 15.6 (SD=2.6) mmHg.

We used only the pressure response as a criterion of success, while many other studies have also included stable visual field and optic disc in the definition of successful treatment. In our series two patients experienced deteriorating visual fields and one progressive cupping of the optic nerve head in spite of normal intraocular pressure without medication.

None of the other studies on primary LTP evaluated their results by lifetime data analysis as recommended by Gaasterland.²⁰ To make our results comparable with these reports we also included all patients, both successes and failures, up to the date of their last clinical visit. The mean follow-up of the material when evaluated in this manner was 34 (SD=13) months. Our results are compared with those of other studies in Table 2.

High prelaser IOP and visual field defect score were predictors of treatment failure ($p < 0.05$). Table 3 presents the success rate at different levels of prelaser IOP. Age, sex, capsular or simple glaucoma, 180° × 2 versus 360° treatment, laser power, or the cup-disc ratio did not influence the outcome of treatment significantly.

The rate of complications and postlaser pressure elevations have been recorded elsewhere.^{11,12}

Discussion

Our results are compared with those of other reports on primary LTP in Table 2. None of these studies have evaluated their results by lifetime data analysis. These investigations differ

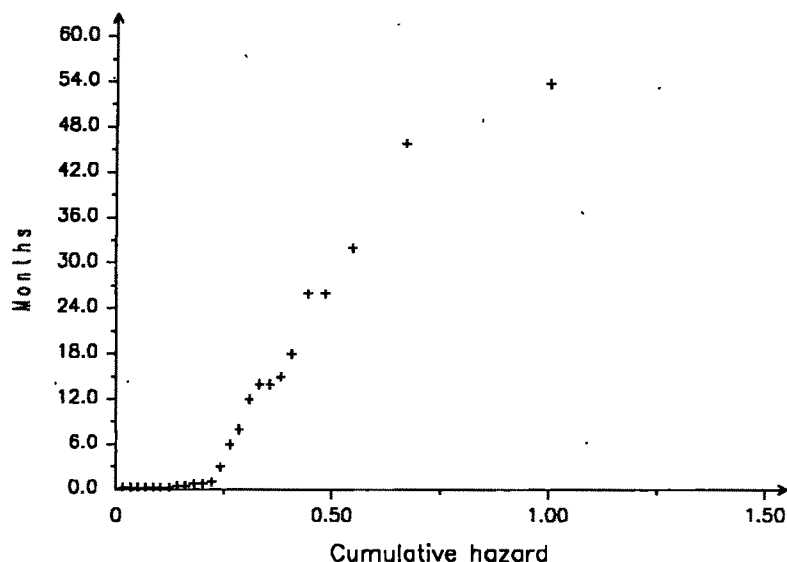


Figure 2 Plot of cumulative hazard with time since treatment with primary LTP. The curve indicates an initially decreasing failure rate and an increasing failure rate towards the end of the observation period.

regarding prelasar IOP, the severity of the disease, and the percentage of capsular glaucoma, and are not directly comparable. Prelasar IOP varies between 24.0 and 35.2 mmHg.

Table 3 Prelasar IOP related to the success rate in primary LTP

Prelasar IOP mmHg	Success rate: number of successful eyes/total number of eyes (%)
≥ 40	4/12 (33%)
< 40	
≥ 30	26/37 (70%)
< 30	
≥ 25	7/11 (64%)

The longterm studies of Tuulonen *et al*⁶ and Migdal and Hitchings⁷ are not directly comparable to ours. The material of Tuulonen *et al* contains only cases of early glaucoma with a considerably lower prelasar pressure than in our study. They reported that 50% were successfully treated after five years. Migdal and Hitchings's cases consisted exclusively of simple glaucoma, while our study has a majority of capsular glaucoma. Their prelasar IOP of 34.9 mmHg was comparable with ours. In their material 44% were successfully treated after a follow-up period varying between seven months and three years. After four years 50% were successful in our study.

The failure rate pattern indicates that the first month after treatment is critical in the sense that the majority of eyes which are susceptible to

Table 2 Six studies on primary LTP compared with the present report

	Follow-up (months)	Number of eyes	Type of glaucoma	Prelasar IOP (mmHg)	Success rate (%)
Tuulonen <i>et al</i> ⁶	12	21	Glaucoma simplex	25.6 (SD=0.9)	81
	18	18	Glaucoma simplex	25.1 (SD=0.7)	78
	12	42	Glaucoma capsular	27.0 (SD=0.7)	100
	18	34	Glaucoma capsular	27.3 (SD=0.7)	94
Thomas <i>et al</i> ⁸	3-10	30	Mostly glaucoma simplex	30.3	83
Rosenthal <i>et al</i> ⁹	6-18.5	43	Glaucoma simplex	Among successes	65
			First eye treated	30.7 (SD=1.3)	
			Second eye treated	29.7 (SD=1.9)	
Tuulonen <i>et al</i> ⁷	12	19	Among failures	34.1 (SD=2.0)	53
			29.4 (SD=7.6)		
Migdal and Hitchings ⁷	7-36	57	Glaucoma capsular and simplex	34.9	44
Tuulonen <i>et al</i> ⁶	60	32	Glaucoma simplex	24.0 (SD=3.1)	50
			Glaucoma simplex	26.4 (SD=3.7)	
			Glaucoma capsular	35.2 (SD=6.5)	
Present study	12	60	Glaucoma capsular and simplex		76
	24	50			64
	36	25			52
	48	12			50

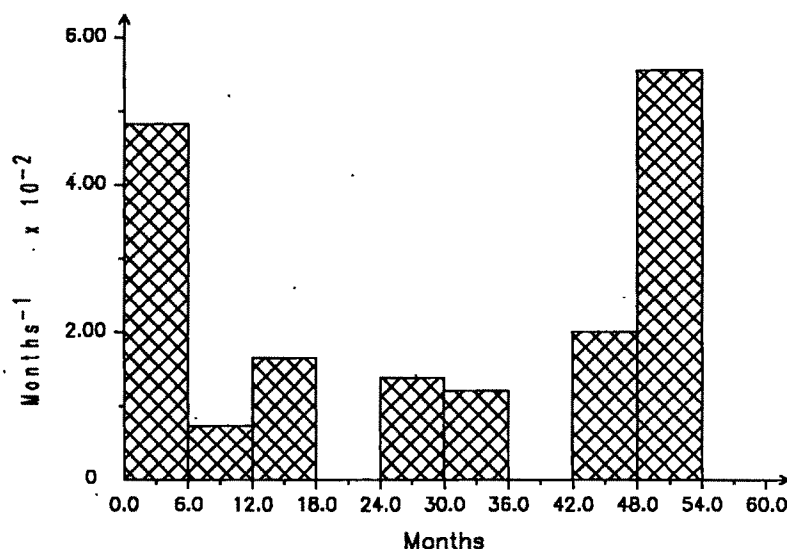


Figure 3 Estimated failure rate in time intervals after primary LTP.

failure in the first year will fail during the first month, and success beyond one month considerably increases the probability of long lasting success. Our observations show, however, that the failure rate increases after four years of success. So, although the data are sparse, they suggest an increasing failure probability after a rather stable level from one month to about four years after treatment. Shingleton *et al*,²¹ studying patients with glaucoma on medication, noted a failure rate of 23% during the first year after LTP, which then levelled off to about 10% per year.

Only Rosenthal *et al*⁹ have analysed prognostic factors in primary LTP. They observed, as in our study, that high pretreatment intraocular pressure was associated with treatment failure. The degree of glaucomatous damage, in contradiction to our results, did not influence the

results of LTP in their material. They also noted that well delineated angle landmarks were a predictor of success. The date of treatment was also correlated with successful treatment. Of the first 15 patients four were successes, while 14 of the final 18 patients were successes. This fact was interpreted as increased success when gaining experience with the procedure. All the eyes in our material were treated by the same experienced laser surgeon. We did not relate chamber angle parameters to treatment results.

There are several studies of the effect of different prelaser variables on the outcome of LTP in glaucoma patients on medication.^{1-3 21-29}

These studies differ regarding the factors influencing the result of treatment. Possible explanations of their contradictory results are that some of the series were too small, some authors did not apply lifetime data analysis, some series contained different types of glaucoma, and different criteria for success were adopted; moreover the values of some parameters were clustered round a median value and did not extend over a wider range. Age^{3 22 25 26} and capsular glaucoma^{23 24 28} are the factors most consistently related to the outcome of treatment by other authors. Schwartz *et al*²² and Tuulonen *et al*²³ reported that high prelaser pressure was a predictor of failure in glaucoma patients on medication. This was supported by our findings. Some reported observations indicate that, as in our material, the severity of the disease may be of importance. In a long-term study Wise² found that eyes with a cup-disc ratio ≥ 0.9 had a surgery rate of 51% compared with 16% in eyes with less advanced damage of the optic nerve head. Tuulonen *et al* noted that primary LTP gave better results than laser treatment in eyes already on medication.²³ In their patients eyes treated with primary LTP were in an earlier stage of the disease than eyes already on medication. This may indirectly suggest that the severity of the disease is also of importance.

In our opinion LTP should be considered as an alternative to medication for the initial treatment of glaucoma. The probability of success after four years is 0.50 even in a group of eyes with a mean prelaser IOP of 35.2 mmHg. There is a high failure rate during the first month after LTP, presumably owing to a group of eyes not responding to laser treatment. Given success one month after treatment, the probability of success increases to 0.63 after four years. The treatment is easy to perform, the complication rate is low, there are no compliance problems as with medication, and the treatment is not expensive. All stages of the disease respond to treatment. On the other hand the severity of the visual field

defects and high prelaser IOP are negative prognostic factors.

- 1 Wise JB. Long-term control of adult open angle glaucoma by argon laser treatment. *Ophthalmology* 1981; **88**: 197-202.
- 2 Wise JB. Ten year results of laser trabeculoplasty. Does the laser avoid glaucoma surgery or merely defer it? *Eye* 1987; **1**: 45-50.
- 3 Ticho U, Neshor R. Laser trabeculoplasty in glaucoma. *Arch Ophthalmol* 1989; **107**: 844-6.
- 4 Rosenthal AR, Chaudhuri PR, Chiapella AP. Laser trabeculoplasty primary therapy in open-angle glaucoma. *Arch Ophthalmol* 1984; **102**: 699-701.
- 5 Thomas JV, El-Mofty A, Hamdy EE, Simmons RJ. Argon laser trabeculoplasty as initial therapy for glaucoma. *Arch Ophthalmol* 1984; **102**: 702-3.
- 6 Tuulonen A. Laser trabeculoplasty as primary therapy in chronic open angle glaucoma. *Acta Ophthalmol (Kbh)* 1984; **62**: 150-5.
- 7 Tuulonen A, Koponen J, Alanko HI, Airaksinen PJ. Laser trabeculoplasty versus medication treatment as primary therapy for glaucoma. *Acta Ophthalmol (Kbh)* 1989; **67**: 275-80.
- 8 Migdal C, Hitchings R. Control of chronic simple glaucoma with primary medical, surgical and laser treatment. *Trans Ophthalmol Soc UK* 1986; **105**: 653-6.
- 9 Tuulonen A, Niva A-K, Alanko HI. A controlled five-year follow-up study of laser trabeculoplasty as primary therapy for open-angle glaucoma. *Am J Ophthalmol* 1987; **104**: 334-8.
- 10 Glaucoma Laser Trial Research Group. The glaucoma laser trial. Acute effects of argon laser trabeculoplasty on intraocular pressure. *Arch Ophthalmol* 1989; **107**: 1135-42.
- 11 Elsäas T. Primary lasertrabeculoplasty: a comparison of 50 spots in 180° and 100 spots in 360° of the trabecular meshwork. *Acta Ophthalmol (Kbh)* 1987; **65**: 323-5.
- 12 Elsäas T, Johnsen H, Brevik TA. The immediate pressure response to primary laser trabeculoplasty - a comparison of one and two-stage treatment. *Acta Ophthalmol (Kbh)* 1989; **67**: 664-8.
- 13 Schwartz B. Cupping and pallor of the optic disc. *Arch Ophthalmol* 1973; **89**: 272-7.
- 14 Kidd MN, O'Connor M. Progression of field loss after trabeculectomy: a five-year follow-up. *Br J Ophthalmol* 1985; **69**: 827-31.
- 15 Aulhorn E. Visual field defects in chronic glaucoma. In: Heilman K, Richardson KT, eds. *Glaucoma: conceptions of a disease*. Stuttgart: Thieme, 1978; 157-68.
- 16 Laless JF. *Statistical models and methods for lifetime data*. New York: Wiley, 1982: 343-400.
- 17 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53**: 457-81.
- 18 Cox DR. Regression models and life tables. *J R Stat Soc B* 1972; **34**: 187-220.
- 19 Wilkinson L. *SYSTAT: The system for statistics*. Evanston: SYSTAT Inc 1988.
- 20 Gaasterland DE. A review of surgical alternatives to medical therapy for glaucoma. *J Natl Med Assoc* 1988; **80**: 721-3.
- 21 Shingleton BJ, Richter CU, Bellows AR, Hutchinson BT, Glynn RJ. Long-term efficacy of argon laser trabeculoplasty. *Ophthalmology* 1987; **94**: 1513-8.
- 22 Schwartz AL, Kopelman J. Four-year experience with argon laser trabecular surgery in uncontrolled open-angle glaucoma. *Ophthalmology* 1983; **90**: 771-80.
- 23 Tuulonen A, Airaksinen PJ, Kuulasmaa K. Factors influencing the outcome of laser trabeculoplasty. *Am J Ophthalmol* 1985; **99**: 388-91.
- 24 Bergeä B. Intraocular pressure reduction after argon laser trabeculoplasty in open-angle glaucoma. *Acta Ophthalmol (Kbh)* 1986; **64**: 401-6.
- 25 Safran MJ, Robin AL, Pollack IP. Argon laser trabeculoplasty in younger patients with primary open-angle glaucoma. *Am J Ophthalmol* 1984; **97**: 292-5.
- 26 Zborowski L, Ritch R, Podos SM, Boas R. Prognostic features in laser trabeculoplasty. *Acta Ophthalmol (Kbh)* 1984; **62**: 142-9.
- 27 Grinich NP, Van Buskirk EM, Samples JR. Three-year efficacy of argon laser trabeculoplasty. *Ophthalmology* 1987; **94**: 858-61.
- 28 Traverso CE, Spaeth GL, Starita RJ, Fellman RL, Greenidge KC, Poryzees E. Factors affecting the result of argon laser trabeculoplasty in open-angle glaucoma. *Ophthalmic Surg* 1986; **17**: 544-9.
- 29 Schwartz AL, Love DC, Schwartz MA. Long-term follow-up of argon laser trabeculoplasty for uncontrolled open-angle glaucoma. *Arch Ophthalmol* 1985; **103**: 1482-4.

Mastering the infant donor eye: a new device for obtaining corneoscleral buttons for storage and corneal discs for keratoplasty

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Abstract

The design and use of a new device for obtaining corneoscleral buttons for storage and corneal discs for keratoplasty from neonatal and adult donor eyes is described. The device is simple to use and eliminates most of the difficulties in handling infant donor eyes. It thus minimises the risk of damage to the corneal endothelium and the formation of stretch striae, which reduce the quality of the donor material for transplantation.

The cornea of infant donors is difficult to handle because of its flexibility and the tendency for the tissue to fold over on itself.^{1,2} This, in addition to the lack of appropriate instruments for handling infant donor eyes during excision of corneoscleral buttons for storage, predisposes the endothelium to risk of damage. Because the infant donor eye may be too small to fit currently available commercial eye stands, it can be wrapped in gauze and hand held for corneal excision. This technique requires great skill, may be imprecise, and may lead to endothelial cell damage. We³ and other investigators^{3,4} have shown that this damage may be in the form of endothelial stretch striae or loss of the posterior membrane of the corneal endothelial cell,^{2,5} which reduces the quality of the donor material for transplantation.

Given the limitations of existing eye stands which can be modified, and the fact that an increasing number of surgeons now employ infant donor corneas for transplantation,⁶⁻⁸ a new device has been designed, produced, and tested with several donor eyes (age range 5 days-98 years) which can be used to hold the enucleated eye of full-term babies and adult donors for excision of corneoscleral buttons and corneal discs. A case is reported to show the value of the new device over the hand held technique of corneoscleral button excision.

Description

The device (Fig 1) comprises a base, main body, eye support block, and a clamping unit. The base consists of a solid circular plate 11.4 cm in diameter, 2.5 cm thick, and weighing 0.7 kg. Its upper surface bears an antifriction disc and has a threaded hole in the centre, extending into the base plate. Into this hole fits the threaded shank of a locating pin. The cylindrical head of the latter forms a fixed spindle by which the main body is mounted on to the base plate and is allowed to rotate.

The main body consists of a solid cylindrical

base with a smooth surface. It is closed at the base except for a central aperture to fit over the locating pin. Projecting upwards from this base is an externally threaded, hollow cylinder, of a narrower diameter, defining a socket which houses the eye support block. A screw threaded radial hole extends into the base of the main body, from a point about 2 mm below its top edge, to receive a screw threaded locking pin. The locking pin has a head by which the pin may be rotated into engagement with the locating pin to lock the main body from rotation.

The eye support is a solid cylindrical block, hollowed out at its upper end. It has an axially extending threaded hole for accommodating the optic nerve stump of the donor eye. There are two interchangeable eye support blocks – a longer one for infant donor eyes and a shorter for use with adult donor eyes.

A threaded manipulating pin knurled at one end fits into the screw threaded hole in the eye support block and can be used to lift the latter out of the main body. When not in use, the manipulating pin can be stored in a blind storage hole at the side of the base plate.

A clamping unit for clamping the donor eye placed on the eye support comprises a lower cylindrical clamping sleeve and an upper clamping ring. The clamping sleeve is a hollow

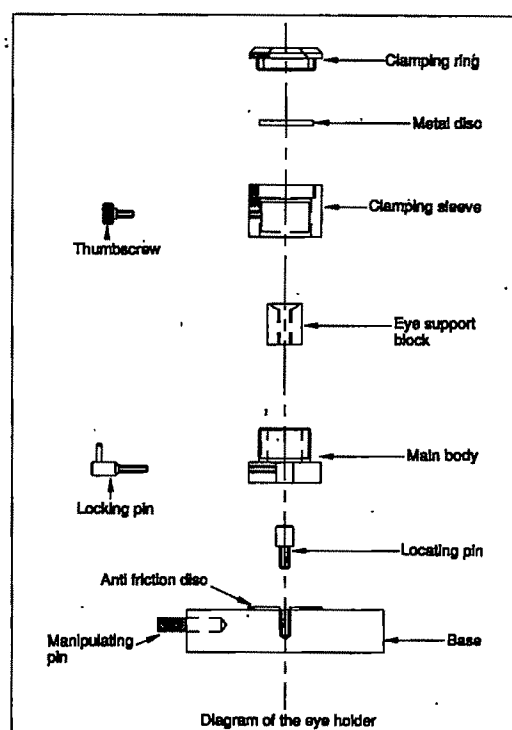


Figure 1 Diagram of the eye holder.

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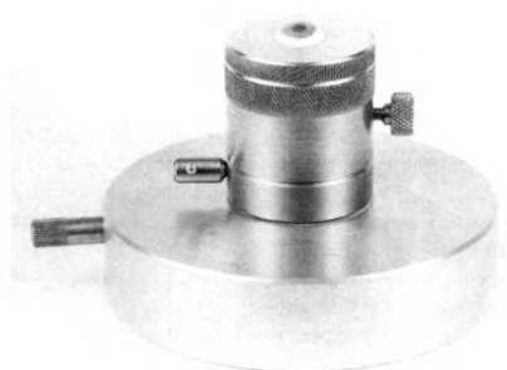


Figure 2 The device with an infant donor eye in situ.

cylinder, knurled at the upper third of its outer surface. It is divided internally into two unequal compartments by an annular ledge, above and below which are screw threads. The lower and deeper threads meet the external threads on the cylindrical projection of the main body, while the upper and shallower threads co-operate with external threads on the skirt of the clamping ring.

The latter is a broad ring with a central, circular aperture through which the cornea and a rim of sclera of the donor eye project as the clamping unit is screwed home on to the main body.

Two interchangeable clamping rings are provided; one with a small central aperture for infant donor eyes and another with a larger aperture for use in obtaining corneoscleral buttons from adults, though the clamping ring intended for infants may also be used for adult donor eyes. The clamping unit acts as an intra-ocular pressure adjuster which applies increasing compression to the donor eye as the clamping unit is screwed on to the main body.

A threaded thumbscrew fits into a threaded hole, half way up the side of the clamping sleeve, to lock the clamping unit to the main body projection.

With the clamping ring and eye support block removed, a metal disc may be placed in the upper compartment of the clamping sleeve, on the annular ledge, to act as a platform for a silicone rubber block for supporting a corneoscleral



Figure 4 Adult donor eye supported in the infant block.

button to be punched out from the endothelial side of the button.

Mode of use

To prepare a corneoscleral button from an infant donor eye for storage

The main body, the infant eye support block, and the clamping sleeve are assembled on the base plate and the main body locked against rotation by the locking pin. The donor eye is cleansed and placed on the eye support with the optic nerve stump extending into the hole in the eye support block. The clamping ring is then screwed home and, provided the clamping sleeve has not engaged more than about half of the threads on the main body projection, the clamping ring will still be clear of the surface of the cornea.

By carefully screwing the clamping unit home clockwise with the thumbscrew, the cornea and a generous rim of sclera will present through the aperture in the clamping ring (Fig 2). When a suitable pressure is judged to have been reached, the thumbscrew is tightened to lock the clamping unit to the main body projection, and the locking pin is released. Rotating the assembly by the locking pin, with the eye engaged by a sharp blade in a holder, allows a simple and atraumatic incision to be made into the suprachoroidal

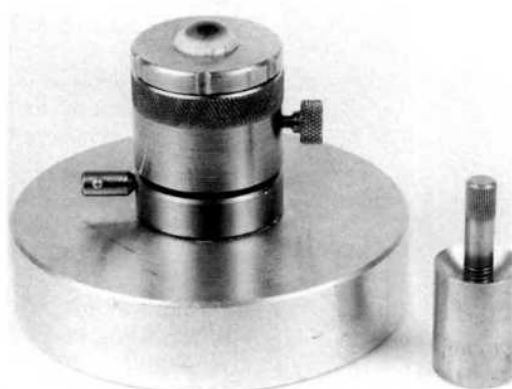


Figure 3 Adult donor eye in situ. Note replaced clamping ring, and infant eye support block with manipulating pin.



Figure 5 Set-up for punching a penetrating donor disc from the endothelial surface.

space. Excision of the corneoscleral button is completed with a corneal scissors and the ciliary body attachments gently separated from the scleral spur.

Removal of a corneoscleral button from the adult donor eye

To remove a corneoscleral button from an adult donor eye the same procedure is followed as for the infant donor eye except that the shorter eye support block and clamping ring with the larger aperture are used (Fig 3). The infant eye support block may, however, be used for adult eyes, provided the clamping sleeve has not engaged more than two-thirds of the threads on the main body projection (Fig 4). If the clamping ring cannot be screwed home over the donor eye, the clamping sleeve may be unscrewed slightly to clear the surface of the cornea. The clamping ring is then screwed home. Which clamping ring is used for the adult donor eye depends on how large a corneoscleral button is required. The clamping ring with the larger aperture cannot, however, be used for the infant donor eye.

To cut a penetrating or lamellar disc from a donor eye

The donor eye is placed in the same assembly as for obtaining a corneoscleral button. A forceps is used to centre the donor eye on the central axis of rotation, and, when a suitable tension for trepanation or lamellar dissection is judged to

have been reached, the thumbscrew is tightened.

Lamellar dissection or trephination can then be carried out in the conventional manner at a constant pressure. After the anterior chamber has been entered, if the trephine is incomplete it may then be completed with a suitable sharp blade or scissors.⁹ The clamping unit and the main body can be rotated as a single unit during the procedure by means of the released locking pin.

Punching a penetrating donor disc from the endothelial surface

The main body and the clamping sleeve are assembled on the base plate without the eye support block and clamping ring, and the main body locked against rotation with the locking pin. The clamping sleeve is screwed home to the fullest extent on the main body projection and the thumbscrew tightened. The metal support disc is then placed in the upper compartment of the clamping sleeve so as to rest on the annular ledge. A silicone rubber block with a concave upper surface is then rested on the metal disc. The corneoscleral button is centred on the silicone block, endothelial surface uppermost (Fig 5), and punched out with a hand held trephine.

Case report

To show the value of the device in minimising stria formation in comparison with the hand held technique of corneal excision, a pair of donor eyes from a 3-week old baby was used as an example. The cause of death was respiratory failure, and the globes were enucleated 12 h post mortem after storage at 4°C. The ocular history was normal for both eyes.

Each eye was examined 2 h after enucleation with the slit-lamp and the wide field specular microscope (the Pocklington, Keeler/Konan), particularly for striae and folds, before corneoscleral button excision, but none were found except for a haze of corneal oedema. Both eyes were rinsed in 0.9% normal saline and the conjunctiva was removed. The right eye was wrapped in gauze and hand held for corneoscleral button excision by the recommended standard technique.¹⁰ Some difficulty was encountered during initial incision into the suprachoroidal space and separation of the ciliary body from the scleral spur. This resulted in distortion of the cornea. There was no loss of the anterior chamber (AC).

The corneoscleral button was placed endothelial surface uppermost on a Teflon plate with a concave surface and stained immediately with Janus green and then with alizarin red S as described by van Delft and colleagues¹¹ and Taylor and Hunt.¹² Light microscopy and photography were performed on the button to evaluate the type and extent of endothelial damage.

The fellow eye (left) was supported in the new device and excised by the recommended technique.¹⁰ There was no loss of the AC. Removal of the corneoscleral disc was relatively easy, as both hands were free to carry out the procedure with minimal distortion to the cornea.

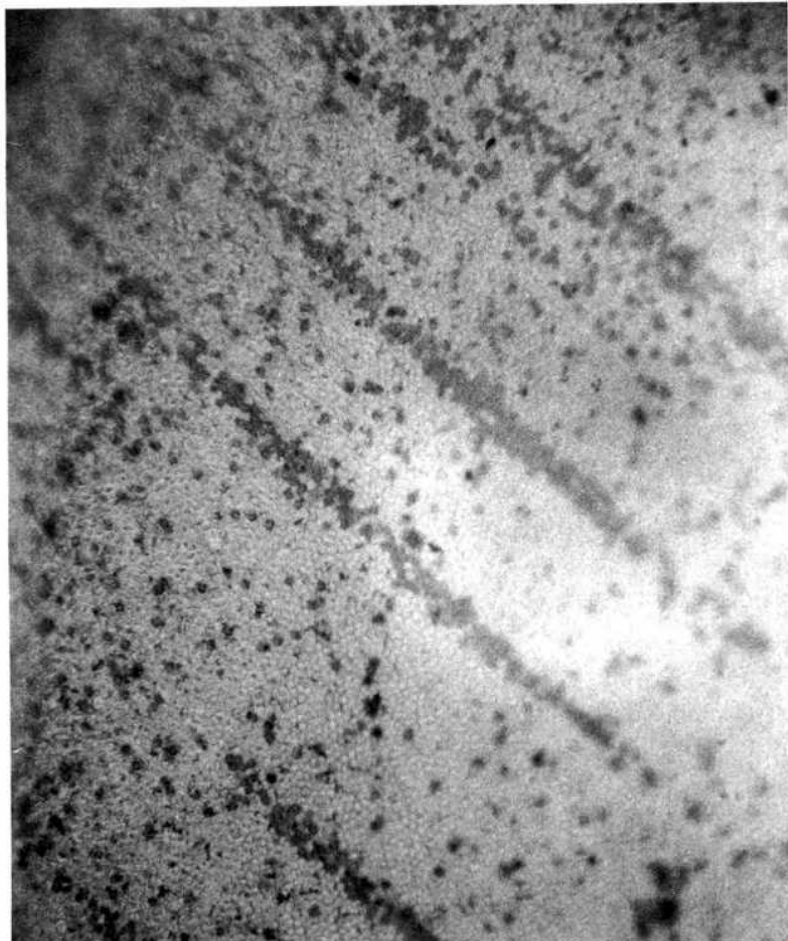


Figure 6 Right eye: hand held for corneoscleral button excision. Note multiple endothelial striae and numerous isolated damaged or dead cells with dark blue staining of the nuclei. (Janus green/alizarin red S stains, $\times 50$.)

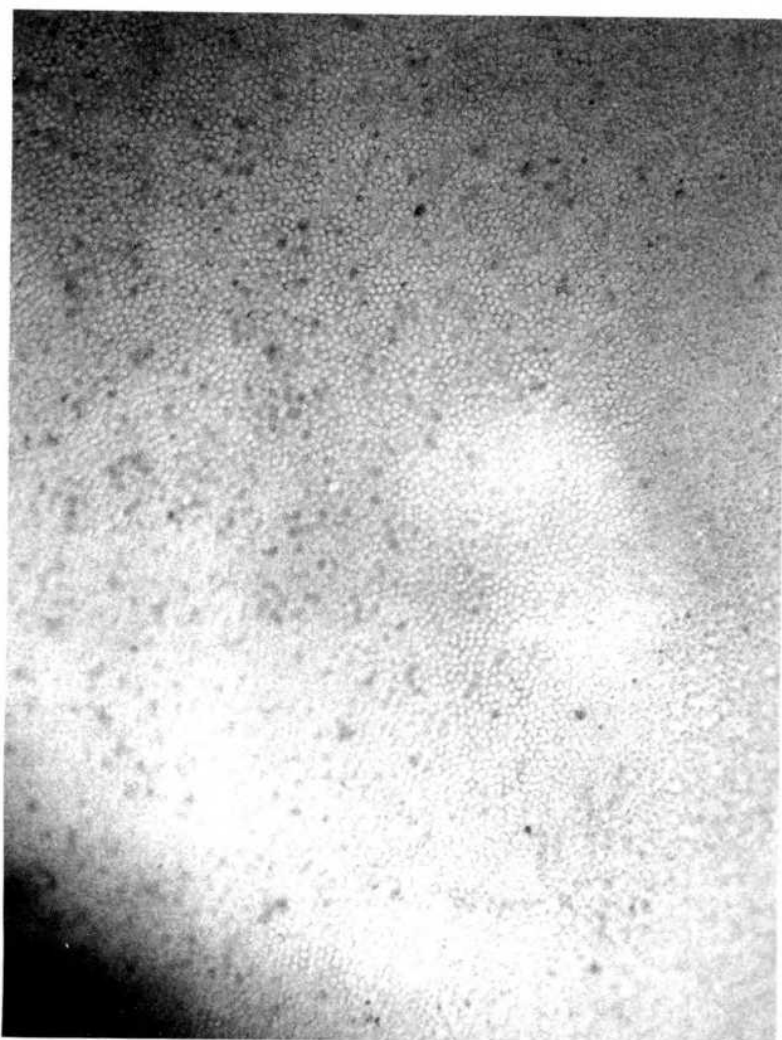


Figure 7 Left eye: supported in new device for corneoscleral button excision. Endothelial striae are absent. Staining of the intercellular borders with alizarin red S shows the mosaic pattern of normal cells. Few isolated damaged cells are present. (Janus green/alizarin red S stains, $\times 50$.)

The left button was similarly stained, examined, and photographed.

Light microscopy of the right button revealed multiple parallel lines of endothelial cells with darkly stained nuclei (Fig 6). In addition, there were areas of normal appearing endothelium interspersed with numerous isolated cells with darkly stained nuclei. Higher magnification showed that these lines corresponded to areas of endothelial cell damage or death as described elsewhere.² The left button showed large areas of intact endothelium outlined by alizarin red S and fewer isolated cells with darkly stained nuclei, but there were no striae (Fig 7).

Discussion

A number of surgeons do not transplant tissue from donors less than 3 years of age because of handling difficulties and the rapid change in corneal power during infancy, which decreases predictability.¹ Nevertheless, others use infant donor corneas for transplantation in aphakic patients.⁶⁻⁸

Damage to the endothelium during excision of corneoscleral buttons from infant donor eyes for storage and their subsequent use for transplantation has been quantified and discussed elsewhere.² If the use of tissue from such donors for transplants is to be encouraged, it would be desirable to have the appropriate instruments for their handling in order to protect the endothelium

from risk of damage. To this end, the author has devised an eye holder suitable for infant donors which leaves both hands free for the excision procedure in a controlled manner and allows better management of complications which may arise. It is believed that this innovation is an advance. The device is simple to use and has the added advantage that it can be used for adult donor eyes and corneal transplant procedures.

A comparative discussion of currently available eye stands is beyond the scope of this article. However, it is worth noting that the design of the device described here incorporates ideas from the Steele-Pierse eye stand,⁹ which is widely used, and provides good support for a wide range of donor eyes.

Janus green gives a more pronounced staining result and better contrast between non-vital and vital cells than trypan blue.¹³ The demarcation of non-vital from vital cell is further improved by counterstaining with alizarin red S. Thus Janus green can replace trypan blue in combined trypan blue/alizarin red S staining as shown by van Delft *et al.*¹¹

Vital staining of the right cornea showed multiple striae at the level of the endothelium but none in the fellow cornea. It is tempting to conclude that the striae in the right cornea were the result of the handling difficulties encountered in the hand held excision technique. However, since no striae or folds were found at slit-lamp and specular microscopy, of both eyes, before corneoscleral button excision, it is reasonable to assume that indeed this is the case.

Although no striae were found in the left cornea, some stria formation is inevitable, even with the best technique.^{2,4} Care should therefore be taken during corneal excision to preserve the maximum number of viable endothelial cells for transplantation.

I thank Mr Arthur D McG Steele for helpful suggestions and for reading the manuscript; Duncan Stamp and Paul Johnson for technical assistance; and Paul Grogan for the photographic processing. I am also grateful to Dr Emil Sherrard for encouragement.

- 1 Wilson SE, Bourne WM. Corneal preservation. *Surv Ophthalmol* 1989; 33: 237-59.
- 2 Nartey IN, Sherrard ES, Steele ADMcG. Manipulative damage to the endothelium of infant and adult donor corneas. *Br J Ophthalmol* 1990; 74: 261-4.
- 3 Roozitalab MH, Requard JJ, Fogle JA, Green WR, Graham CR Jr. Endothelial stretch striae in donor corneas: cause, significance, and prevention. *Md Med J* 1979; 28: 47-55.
- 4 Grutzmacher RD, Oiland D, McKillop BR, Bunt-Milam AH. Donor corneal endothelial striae. *Am J Ophthalmol* 1986; 102: 508-15.
- 5 Polack FM. Penetrating keratoplasty. In: Polack FM, ed. *Corneal transplantation*. New York: Grune and Stratton, 1977: 135-46.
- 6 Pfister RR, Breard S. Aphakic refractive penetrating keratoplasty using newborn donor corneas. *Ophthalmology* 1983; 90: 1207-12.
- 7 Wood TO, Nissernkorn L. Infant donor corneas for penetrating keratoplasty. *Ophthalmic Surg* 1981; 12: 500-2.
- 8 Fong LP, Gladstone D, Casey TA. Corneoscleral rim cultures: donor contamination. A case of fungal endophthalmitis transmitted by K-sol cornea. *Eye* 1988; 2: 670-6.
- 9 Steele ADMcG, Pierse D. Mastering the donor eye: a new device for obtaining corneal discs. *Br J Ophthalmol* 1978; 62: 86-8.
- 10 Krachmer JH Jr. *Medical Standards of the Eye Bank Association of America*. 1984; section 8:1.
- 11 van Delft J, Oosterhuis J, Barthen E, Eijkelenboom A. Janus green vital staining of the cornea. *Doc Ophthalmol* 1983; 55: 47-50.
- 12 Taylor MJ, Hunt CJ. Dual staining of corneal endothelium with trypan blue and alizarin red S: importance of pH for the dye-lake reaction. *Br J Ophthalmol* 1981; 65: 815-9.
- 13 Hartman C, Rieck P. A new test for endothelial viability. The Janus green photometry technique. *Arch Ophthalmol* 1989; 107: 1511-5.

Clinical evaluation of automated refraction in anterior chamber pseudophakia

Palaniswamy Sunder Raj, Jose R Villada, Kyaw Myint, Anne E Lewis, Tayo Akingbehin

Abstract

Automated refraction with the Canon RK-1 Autoref keratometer was evaluated in 85 eyes of 85 patients with an anterior chamber intraocular lens implant and a best corrected visual acuity of at least 6/12. Autorefraction readings were obtained in 80 (94%) of these eyes. The agreement between autorefraction and clinical refraction data was 89% for spherical equivalence <0.51 dioptres (D), 91% for sphere power <0.51 D, 82% for cylinder power <0.51 D, and 91% for cylinder axis $<11^\circ$. Autorefraction provides acceptably accurate postoperative refraction values in anterior chamber pseudophakia.

Autorefractors (ARs) are being increasingly used in busy ophthalmology clinics because they can be operated by a nurse or technician,¹ are much quicker than manual refraction,^{1,2} and are highly esteemed by most patients.¹ Objective autorefraction can provide reliable and valid preliminary refraction data,¹⁻¹² especially in subjects who do not possess 'true' accommodation due to aphakia,^{2,13} pseudophakia,¹⁴ or cycloplegia.^{12,15,16}

Intraocular lenses (IOLs) can interfere with the accuracy of objective ARs^{1,9,10,17} by scattering the measuring infrared beam and increasing 'noise'.^{10,17} Modern ARs overcome this problem by providing an 'IOL setting' which improves the signal-to-noise ratio in the recording system while refracting pseudophakes. We evaluated the use of one such instrument, the Canon RK-1 Autoref keratometer, in patients with posterior chamber IOLs and found it to be acceptably accurate.¹⁴ In this paper we report on the use of the same AR in patients with anterior chamber IOLs.

Patients and methods

INSTRUMENT

The Canon RK-1 Autorefkeratometer combines both automated refraction and keratometry in one instrument. The optical principle on which it operates, its capacity to refract, special facilities possessed, and the method used to measure refraction with this instrument have been detailed in a previous communication.¹⁴

PATIENTS AND EYES

This study was carried out on patients who had undergone anterior chamber IOL implantation in one or both eyes. Of the 102 such patients seen consecutively in the eye clinic 99 had unilateral anterior chamber IOLs and three were bilateral. For the purposes of this study we included only

the right eyes of the patients with bilateral anterior chamber IOLs, giving us 102 eyes of 102 patients. Seventeen eyes were excluded because they did not attain a best corrected visual acuity of at least 6/12. Of the remaining 85 eyes studied, valid AR values could not be obtained owing to various causes in five eyes, leaving 80 eyes of 80 patients for analysis.

METHODS

All the refractions, clinical as well as on the autorefractor, were carried out without the use of mydriatics. Clinical refraction, streak retinoscopy followed by subjective verification, was carried out by two of the authors (PSR, KM) to achieve the best possible visual acuity. Autorefraction was performed to obtain a series of three readings by a different examiner (AEL). The 'standard' refractive value in the AR print-out data (categorised into reliable and less reliable data) was then compared with the result of clinical refraction for degree of agreement.

STATISTICAL ANALYSIS

The statistical significance of the difference between the less reliable (indicated by the 'reliability mark') and reliable autorefractive data was evaluated using two tests: (1) χ^2 test on the number of eyes in the two groups within 0.51 D of spherical equivalence, spherical power, or cylindrical power and within 11° in cylindrical axis as determined by clinical refraction; and (2) standard error of the difference between means on the mean difference in the various refractive components between automated and conventional refraction.

Results

Of the 85 eyes (85 patients) with anterior chamber IOLs which were eligible for the study valid autorefractive data could not be obtained in five eyes. The reasons included inability to keep the eyes focused on the target (two eyes), cylinder value outside the range of the AR, uncontrolled blinking, and inability to extend the neck (one eye each). Clinical refraction of the eye whose cylinder value could not be estimated by the AR revealed a cylinder power of $+5.0$ D.

The percentage agreement between autorefraction and clinical refractive data with respect to the various refractive components is shown in Table 1. 89% of the autorefraction values were within 0.51 D of spherical equivalence, 91% were within 0.51 D of spherical power and 11° of cylindrical axis, and 82% were within 0.51 D of cylinder power. The percentage agreement between the AR and clinical refractive data

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Table 1 Degree of agreement between autorefractive and clinical refractive data of various refractive components

Refractive component	Autorefractor reading: no. (%)		
	Reliable (n=57)	Less reliable (n=23)	Total (n=80)
Spherical equivalent			
±0.25 D	35 (61%)	14 (61%)	49 (61%)
±0.50 D	53 (93%)	18 (78%)	71 (89%)
±1.00 D	56 (98%)	21 (91%)	77 (97%)
Sphere power			
±0.25 D	44 (77%)	14 (61%)	58 (73%)
±0.50 D	56 (98%)	16 (70%)	72 (91%)
±1.00 D	57 (100%)	21 (91%)	78 (99%)
Cylinder power			
±0.25 D	37 (65%)	8 (35%)	45 (56%)
±0.50 D	48 (84%)	18 (78%)	66 (82%)
±1.00 D	55 (96%)	20 (87%)	75 (93%)
Cylinder axis			
±5°	43 (75%)	17 (74%)	60 (75%)
±10°	53 (93%)	20 (87%)	73 (91%)
>10°	2 (4%)	2 (9%)	4 (5%)
*NC	2 (4%)	1 (4%)	3 (4%)

n=Number of eyes (patients).

*No cylinder in one of the methods of refraction.

in the reliable and less reliable autorefractive data groups were compared by the χ^2 test. There was no statistically significant difference between the two AR groups in spherical equivalence ($p>0.05$), cylinder power ($p>0.5$) or cylinder axis ($p>0.3$), but there was a significant difference in sphere power ($p<0.005$).

Autorefractive indicated a cylinder power in three eyes (one in the reliable group and two in the less reliable group) where none was found on clinical testing. The cylinder powers, in dioptres ('plus'), were 0.37, 0.5, and 0.75 respectively.

The mean differences between autorefractive and clinical refraction in spherical equivalence, sphere power, cylinder power, and cylinder axis are shown in Table 2. Spherical equivalence and the cylindrical power were both more myopic or less hypermetropic on the AR compared with conventional refraction unlike the sphere power, which was more hypermetropic or less myopic. The mean difference in cylinder axis was 4.2° (SD 5.2°).

Autorefractive data were categorised into reliable and less reliable values. The differences between mean reliable AR values and clinical refraction data were computed and compared with values derived in a similar fashion for less reliable data. Using the standard error of the difference between the means to assess statistical significance, we found no difference between the two groups in spherical equivalence ($p>0.4$), sphere power ($p>0.2$), cylinder power ($p>0.4$), and cylinder axis ($p>0.6$).

Table 2 Mean difference and standard deviations (SD) between autorefractive and clinical refraction

Refractive component	Autorefractor reading*: mean (SD)		
	Reliable (n=57)	Less reliable (n=23)	Total (n=80)
Spherical equivalent (D)	-0.05 (0.27)	0.05 (0.68)	-0.01 (0.46)
Sphere power (D)	0.00 (0.22)	0.14 (0.55)	0.04 (0.35)
Cylinder power (D)	-0.04 (0.44)	-0.14 (0.55)	-0.02 (0.48)
Cylinder axis (degrees)	4.1 (5.7)	4.6 (5.0)	4.2 (5.2)

n=Number of eyes (patients).

*The minus (-) sign indicates more myopia or less hypermetropia on the autorefractor than by clinical refraction.

Discussion

Extracapsular cataract extraction followed by posterior chamber IOL implantation is the current method of choice in the visual rehabilitation of cataract patients. Anterior chamber IOL implantation is still indicated as a primary procedure where posterior chamber IOL implantation is not possible owing to extensive rupture of the posterior capsule or zonular dehiscence. Secondary implantation in aphakia is usually performed using an anterior chamber IOL. With preoperative ocular biometry the desired postoperative refraction can be achieved by the surgeon in a significant number of pseudophakic eyes.¹⁸ However, ocular refraction will continue to play an important role in the postoperative evaluation of pseudophakic eyes not only for optimising visual acuity but also for managing postoperative astigmatism.

An autorefractometer which can be operated by the nursing staff to provide accurate refraction values in pseudophakes will result in an appreciable saving of the clinician's time. Previous reports on autorefractive in pseudophakic eyes have not been adequately comprehensive¹⁻³ or have dealt exclusively with posterior chamber pseudophakes.¹⁴ Rassow and Wesemann¹ classified results as good, bad, or instrument failure in terms of the visual acuity achieved with the autorefractor reading compared with subjective refraction. Wood¹⁰ found that IOLs accounted for a significant number of unobtainable or rejected AR measurements. Dufier *et al.*² studied a general clinic population which included normal, aphakic and pseudophakic eyes but pseudophakes were not separately analysed.

In this study of anterior chamber IOLs the various autorefractive data in pseudophakic eyes were all acceptably accurate especially as preliminary refraction. Subjective verification of the result was essential before final prescription. A similar outcome with the AR has been reported in posterior chamber pseudophakes¹⁴ and adults and children under cycloplegia.^{15,16} In comparison manifest autorefractive in normal subjects has yielded poorer results for spherical equivalence with percentage agreement with clinical refraction being as low as 41%.¹² This is probably because the inbuilt autofogging mechanism in the AR fails to neutralise adequately the patients' accommodation, producing significant instrument myopia.^{15,16} This phenomenon does not affect aphakes or pseudophakes who lack 'true' accommodation,¹⁹ accounting for autorefractive results which are superior to those observed in subjects with intact accommodation.^{1,2,4-10,12,14,15}

Although differential analysis of the reliable and less reliable AR reading showed a statistically significant difference between the two groups in sphere power, this was not clinically important,^{14,15} as the autorefractive data were considered as preliminary results needing subjective verification.

It is not only the accuracy of the autorefractive measurements that is important but also the percentage of a given number of eyes that can be measured with an AR. AR readings were either invalid or not obtainable in 6% (five out of 85) of the eyes studied where conventional refraction was possible. This is lower than the 25%¹⁰ and

60%⁴ mentioned in previous studies on autorefractometry, which have included pseudophakic eyes, but is in agreement with our study of posterior chamber IOLs.¹⁴

A single eye could not be measured by the AR because the cylinder value was supposedly outside its specified range. On clinical refraction the cylinder power in this eye was +5 D. The cylindrical power determined clinically was less than that indicated objectively by autorefractometry, possibly because the patient with this eye had difficulty in accepting subjectively the high cylindrical correction. Three of the study eyes which had a cylinder power on the AR did not need it on subjective verification. Previous reports^{7,14} have pointed out that cylinder values obtained on the AR were often clinically insignificant.

The clinical impression gained during this evaluation was that autorefractometry was both quick and easy to perform. Although this procedure was not timed and compared with conventional refraction, a saving in the clinician's time of four minutes per eye has been reported in a clinic setting.⁷ The results of this evaluation of the Canon RK-1 Autorefractometer in refracting anterior chamber pseudophakes were consistent with those of our previous study on posterior chamber pseudophakes.¹⁴

We thank Miss Lisa Jones for secretarial assistance.

- 1 Rassow B, Wesemann W. Automatic infra-red refractors. *Ophthalmology* 1984; 91(S): 10-26.
- 2 Dufer JL, Abitbol M, Pigamo F, Prete T, Paris JP, Poitreau O. Automatic objective refractometer: evaluation in 3618 eyes. *J Fr Ophtalmol* 1987; 10: 301-8.
- 3 Guyton DL. Automated refractors - 1983. *Ophthalmology* 1983; 90(S): 36-44.
- 4 French CN, Wood ICJ. The dioptron in practice. *Optician* 1981; 181: 18-30.
- 5 Wong EK, Patella V, Pratt M, Myers S, Gaster R, Irving HL. Clinical evaluation of the Humphrey automatic refractor. *Arch Ophthalmol* 1984; 102: 870-5.
- 6 Wood ICJ, Papas E, Burghardt D, Hardwick G. A clinical evaluation of the Nidek autorefractor. *Ophthalmic Physiol Opt* 1984; 4: 169-78.
- 7 Ghose S, Nayak BK, Singh JP. Critical evaluation of the NR-1000F autorefractometer. *Br J Ophthalmol* 1986; 70: 221-6.
- 8 Reddy NS, Agarwal S. Clinical evaluation of the Topcon autorefractor. *Indian J Ophthalmol* 1987; 35: 407-10.
- 9 Wesemann W, Rassow B. Automatic infra-red refractors - a comparative study. *Am J Optom Physiol Opt* 1987; 64: 627-38.
- 10 Wood ICJ. A review of autorefractors. *Eye* 1987; 1: 529-35.
- 11 Anonymous. Refractors. *Ophthalmology* 1988; 95(S): 171-6.
- 12 Ehrlich DL. The Canon RK-1: refractor mode evaluation. *Ophthalmic Physiol Opt* 1990; 10: 97.
- 13 Guillon M. Automated refraction in aphakia-II. Its repeatability and accuracy compared to conventional techniques. *Ophthalmic Physiol Opt* 1986; 6: 85-9.
- 14 Sunder Raj P, Akingbehin T, Levy AM. Objective autorefractometry in posterior chamber pseudophakia. *Br J Ophthalmol* (in press).
- 15 Nayak BK, Ghose S, Singh JP. A comparison of cycloplegic and manifest refractions on the NR-1000F (an objective autorefractometer). *Br J Ophthalmol* 1987; 71: 73-5.
- 16 Hunold W, Auffarth G, Effert R. Clinical application of the Canon R-10 autorefractor in children with squint. *Klin Monatsbl Augenheilkd* 1988; 192: 58-65.
- 17 Charman WN. Infra-red autorefractors - here to stay? *Ophthalmic Physiol Opt* 1985; 5: 237-9.
- 18 Dang MS, Sunder Raj PP. SRK II formula in the calculation of intraocular lens power. *Br J Ophthalmol* 1989; 73: 823-6.
- 19 Nakazawa M, Ohtsuki K. Apparent accommodation in pseudophakic eyes after implantation of posterior chamber intraocular lenses. *Am J Ophthalmol* 1983; 96: 435-58.



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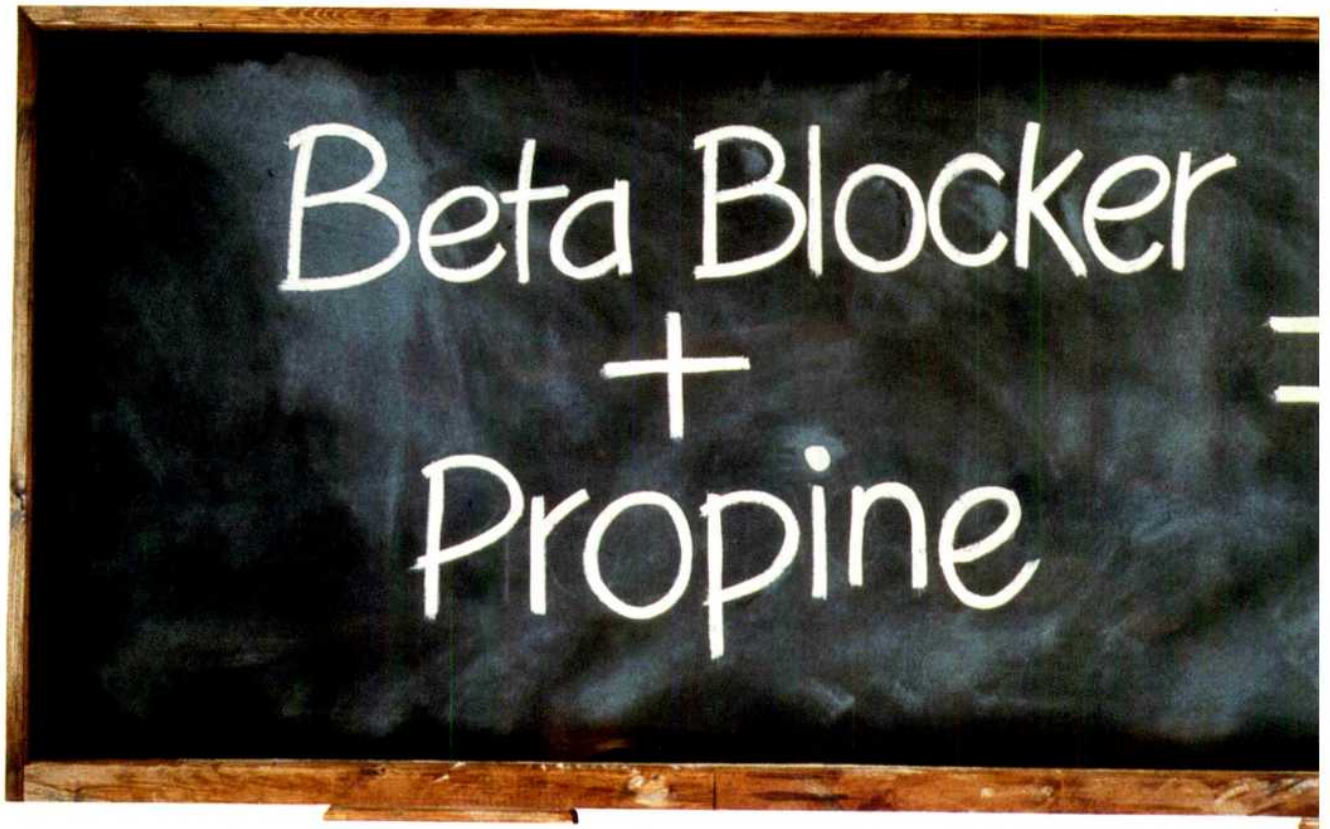
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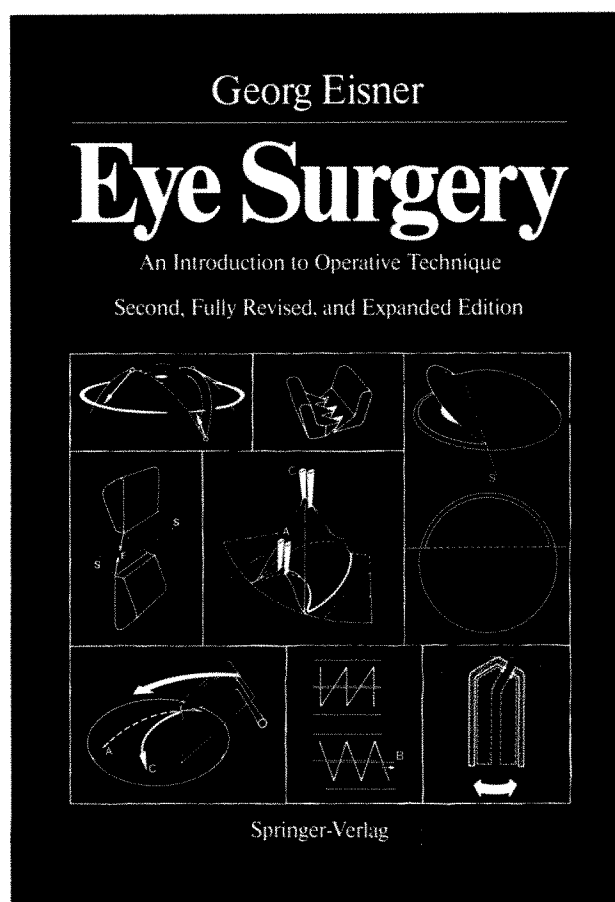
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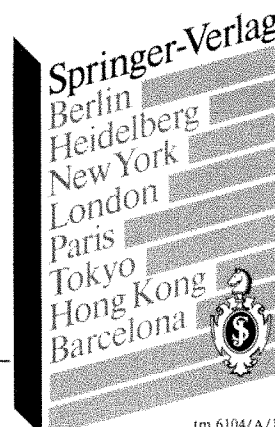


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Pupil cycle time and early autonomic involvement in ocular leprosy

Murat A Karaçorlu, Zeki Sürel, Tülay Çakiner, Erdal Hanyaloğlu, Türkan Saylan, Cem Mat

Abstract

Ocular complications of leprosy patients often develop insidiously and with few if any symptoms. This study involves measurement of the pupil cycle time (PCT) to evaluate the autonomic nerve system of the iris to determine the presence of subclinical intraocular involvement. The study included 19 lepromatous (LL), 19 borderline lepromatous (BL), and five borderline tuberculoid (BT) leprosy patients and involved 83 eyes. The control group included 25 healthy volunteers, 10 patients with pulmonary tuberculosis and eight with Dühring disease. The PCT was measured in these groups. In all leprosy groups included in the study the PCT was higher than in the control groups. Moreover, the PCT of the leprosy patients without any intraocular involvement was higher than in the controls. These results show that in the ophthalmic examination of leprosy patients without any symptoms the fact that autonomic nerve system of the eye is affected by the leprosy can often be determined by measuring the PCT.

Leprosy is a chronic infectious disease primarily affecting the peripheral nervous system and secondarily involving the skin, the mucosa of the mouth and upper respiratory tract, the reticuloendothelial system, eyes, bones, and testes.¹² It is caused by *Mycobacterium leprae* and has been estimated to affect 10 to 15 million people throughout the world.³⁴ In endemic regions a high proportion of the population come into contact with the bacillus, though 95% of these have a normal immune response and therefore do not develop leprosy. Of the remaining 5% some cannot mount any response to the bacteria and so develop lepromatous leprosy (LL). Others develop a hypersensitivity reaction similar to that found in tuberculosis, which is therefore called tuberculoid leprosy (TT).⁵ These are two polar forms of the disease, but a full classification of the disease, put forward by Ridley and Jopling,⁶ includes intermediate forms of leprosy with characteristics of both groups. These are borderline lepromatous leprosy (BL), mid-borderline leprosy (BB), and borderline tuberculoid leprosy (BT).

Most authors would agree that the eye is frequently involved in leprosy, but actual figures vary enormously, from 1% to 100%.⁷ The reasons for these large differences relate either to patterns and features of the disease and its distribution or to the protocol of the studies carried out.⁷

Transmission to the eye is generally thought to be by blood borne infection during a period when organisms are free in the bloodstream, but

this is not entirely certain. For instance, the mycobacteria may reach the eye from the skin of the lids, the meibomian glands, or even from the nose via the lacrimal drainage system.⁸

Mycobacterium leprae probably begin to multiply in the ciliary body, which is richly supplied with blood vessels. They then spread into neighbouring structures such as the iris and cornea by direct extension or along nerve fibres and blood vessels. The bacillus causes destruction of some of the nerve tissue in the ciliary body and iris along with iridocyclitis as a result of its antigenic effect. In the long term, neurotrophic iritis, acute and chronic lepromatous iridocyclitis, and the complications following them are the causes of the patients' becoming blind.⁹

It has generally been accepted that among leprosy patients intraocular involvement occurs often in cases of lepromatous leprosy, less often in borderline lepromatous leprosy, and never in tuberculoid leprosy. Most authors also agree that it is uncommon to see intraocular signs in the first four or five years of the disease. However, if patients with the multibacillary disease remain untreated, an estimated 50% will develop visible eye lesions by the end of the first decade.⁸

ffytche⁹ stated that early involvement of the autonomic nerves in the lepromatous iris, with their eventual destruction, and the late effects of neuroparalysis, include the slow atrophy of the iris muscle and associated chronic low-grade inflammatory changes. He also stated that in the early stages of lepromatous leprosy identification of autonomic involvement could lead to therapy designed to prevent dilator atrophy, with its complication of persistent miosis.

Swift and Bauschard¹⁰ have reported 11 cases of autonomic denervation hypersensitivity among 20 leprosy patients. However, to our knowledge there have been no reports of any testing or measurement methods to quantify subclinical intraocular involvement.

The purpose of this communication is to introduce a method which might be used in diagnosis. A thin slit-lamp beam illuminating the pupil margin produces clearly visible pupil oscillations. These oscillations can be timed with a stopwatch, thus producing a measurement of the 'edge-light pupil cycle time'. The pupil cycle time is remarkably stable in various testing situations and is repeatable. When the optic nerve is normal, the pupil cycle time is dependent on the innervation and integrity of the iris muscle. This study involves measurement of pupil cycle time (PCT) to evaluate the autonomic nerve system of the iris to determine the presence of subclinical intraocular involvement. Besides the leprosy patients we measured the PCT of pulmonary tuberculosis patients taking isoniazid and rifampicin and patients with Dühring disease

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taking dapsone as control groups. We also measured the PCT of healthy volunteers.

Patients and methods

This study included 19 patients with lepromatous leprosy (LL), 19 with borderline lepromatous leprosy (BL), and five with borderline tuberculoid leprosy (BT) and involved 83 eyes. Three patients, two from the LL group and one from the BL group, each had one eye which was not included into the study (two were excised following trauma and one was phthisic as a result of globe perforation). The control group included 25 healthy volunteers, 10 patients with pulmonary tuberculosis taking isoniazid and rifampicin, and eight Duhning disease patients with dapsone. The test was explained and informed consent was obtained. No patient after meeting the entry criteria refused to volunteer.

The type of leprosy was diagnosed according to the Ridley-Jopling⁶ classification on clinical, microbiological and histological basis. All subjects had normal optic nerve function as determined by direct ophthalmoscopic examination, absence of an afferent pupillary defect, and 6/6 best corrected acuity. Leprosy patients with active uveitis, posterior synechiae, or diffuse iris atrophy were not included in the study.

Corneal sensitivity was measured with a Cochet-Bonnet aesthesiometer. Sensitivity was considered to be affected or reduced if two quadrants of the cornea showed more than 10 mm of sensitivity reduction. Pupil cycle time was measured according to Miller and Thompson.¹¹ The mean PCT of each pair of eyes was used in statistical analysis with the exception of three patients whose single eyes were included.

The average age of the LL and BL patients was close to the average age of the control group

39 (SD 11) and ranged from 22 to 61 years. The BT patients' average age was higher than the group as a whole, whereas the average age of the patients with Duhning disease and pulmonary tuberculosis was lower. When the duration of the diseases were investigated, the LL patients' disease duration was found to be on average 21 (SD 11) years, of BL patients 17 (SD 9) years, and of BT patients 14 (SD 9) years. Various characteristics of these groups were shown in (Table 1).

Treatment of 17 (39.6%) of the leprosy patients ended at least three months prior to this study. Treatment of 26 (60.4%) of the patients continued during this study. Subjects from the healthy control group did not use any topical or systemic medicine. Pulmonary tuberculosis and patients with Duhning disease had treatment during the study.

Statistical significance between population samples was determined by the two-tailed Student's *t* test, multiple regression analysis, Pearson's correlation coefficient, and analysis of variance.

Results

Intraocular involvement was found in 16 (37.2%) patients, whereas 27 (62.8%) patients had none. Decreased corneal sensitivity was found in 15 (34.9%) patients and normal sensitivity in the rest, that is, 28 (65.1%). Prominent corneal nerves were noted in 14 (32.6%) patients, corneal nerve beading in 10 (23.3%) superficial punctate keratitis in 5 (11.6%) and a superior quadrants subepithelial corneal scar in 6 (14%). Chronic lepromatous iridocyclitis was found in 14 (32.6%) patients, whereas no symptoms (that is, keratic precipitates, iris atrophy, iris pearl, or sequelae of posterior synechiae) in the rest 29 (67.4%)

Table 1 Group characteristics

	No of subjects	%	Age (yr): mean (SD) [range]	Duration of diseases (yr): mean (SD) [range]	No of eyes female (%)	No of eyes male (%)
<i>Leprosy patients</i>						
Lepromatous leprosy (LL)	19	44.2	37 (13) [16-61]	21 (11) [4-45]	6 (31.6)	13 (68.4)
Borderline lepromatous leprosy (BL)	19	44.2	41 (11) [25-74]	17 (9) [3-35]	2 (10.5)	17 (89.5)
Borderline tuberculoid leprosy (BT)	5	11.6	48 (9) [32-57]	14 (9) [1-25]	1 (20.0)	4 (80.0)
Total	43	100				
<i>Control groups</i>						
Healthy controls	25		39 (11) [22-61]		13 (52.0)	12 (48.0)
Pulmonary tuberculosis	10		34 (9) [19-51]		4 (40.0)	6 (60.0)
Duhning disease	8		30 (6) [21-38]		3 (37.5)	5 (62.5)

Table 2 Distribution of ocular findings in the different types of leprosy patients

	<i>Lepromatous leprosy (n=19)</i>		<i>Borderline lepromatous leprosy (n=19)</i>		<i>Borderline tuberculoid leprosy (n=5)</i>		<i>Total (n=43)</i>	
	No	%	No	%	No	%	No	%
Prominent corneal nerves	7	36.8	7	36.8	—	—	14	32.6
Corneal nerve beading	6	31.6	4	21.0	—	—	10	23.3
Corneal hyperaesthesia	8	42.1	7	36.8	—	—	15	34.9
Superficial punctate keratitis	3	15.8	2	10.5	—	—	5	11.6
Superior quadrants subepithelial corneal scar	5	26.3	1	5.3	—	—	6	14.0
Iris atrophy (mild)	3	15.8	3	15.8	—	—	6	14.0
Iris pearl	2	10.5	1	5.3	—	—	3	7.0
Chronic lepromatous iridocyclitis	10	52.6	4	21.0	—	—	14	32.6

Table 3 Types of leprosy and comparison of pupil cycle times

	Lepromatous leprosy			Borderline lepromatous leprosy			Borderline tuberculoid leprosy			Total
	No of patients (%)	Mean cycle time (SD) (ms)	p Value	No of patients (%)	Mean cycle time (SD) (ms)	p Value	No of patients (%)	Mean cycle time (SD) (ms)	p Value	No of patients (%)
Multidrug therapy*										
Yes	13 (68.4)	1012 (248)	<0.001	13 (68.4)	936 (159)	<0.001	0	—		26 (60.4)
No	6 (31.6)	961 (89)	<0.001	6 (31.6)	1016 (119)	<0.001	5 (100)	915 (145)	<0.001	17 (39.6)
Intraocular involvement										
Yes	9 (47.4)	1086 (282)	<0.001	7 (36.8)	1038 (181)	<0.001	0	—		16 (37.2)
No	10 (52.6)	919 (86)	<0.001	12 (63.2)	924 (132)	<0.001	5 (100)	915 (145)	<0.001	27 (62.8)
Totals	19 (44.2)	1007 (218)	<0.001	19 (44.2)	957 (153)	<0.001	5 (11.6)	915 (145)	<0.001	43 (100)

* Dapsone + rifampicin + clofazimine or prothionamide.

patients. The distribution of ocular findings is shown in Table 2.

When pupil cycle time was studied, the healthy control group had an average PCT value of 820 (47) ms (mean and SD). Pulmonary tuberculosis and Duhning disease patients had average PCT values of 831 (37) ms and 828 (33) ms, respectively. LL patients had an average PCT value of 1007 (218) ms, BL patients had an average PCT value of 957 (153) ms, and BT patients had an average PCT value of 915 (145) ms (Table 3).

The effect of age on PCT was tested in the healthy control group, the pulmonary tuberculosis patients, and the Duhning disease patients was not significant. Nor did age affect the PCT in LL, BL, and BT patients. The effects of the duration of the disease versus PCT was found to be insignificant for LL and BL groups, but for the BT group some dependency was evident ($r=0.667$, $p<0.02$). The PCT of patients with pulmonary tuberculosis and Duhning disease was not significantly different from that of the healthy control group. Finally, the PCT of all leprosy groups versus healthy controls showed a significant difference ($p<0.001$).

LL patients with intraocular involvement had an average PCT value of 1086 (282) ms. BL patients with intraocular involvement had an average PCT value of 1038 (181) ms. The average PCT values of 919 (86) ms and 924 (132) ms were measured in the LL patients without any intraocular involvement and BL patients without any intraocular involvement, respectively. Although the last two PCT values were lower than the ones including patients with intraocular involvement, the difference between them and the PCT in the healthy control group was still statistically significant ($p<0.001$) (Table 3).

Also studied was the PCT difference between two eyes of all the subjects. It was 30 (13) ms when healthy control group subjects were studied, 40 (12) ms when it involved pulmonary tuberculosis group patients, and 36 (11) ms when Duhning disease patients were studied. These

numbers did not differ significantly ($p>0.05$). However, when the PCT difference between two eyes was measured among LL, BL, and BT patients very different values were obtained in comparison with the control group, namely 94 (63) ms, 70 (60) ms, and 83 (66) ms, respectively. Comparison of these values with the PCT difference between the eyes in the controls shows a significant difference ($p<0.001$) (Table 4).

Leprosy patients were divided into two groups, (1) continuing treatment, (2) no treatment (after treatment). In the first group the average PCT value of LL patients was 1012 (248) ms and of BL patients 936 (159) ms. In the second group the average PCT value of LL patients was 961 (89) ms, of BL patients 1016 (119) ms, and of BT patients 915 (145) ms. When these values were compared with the PCT value of the control group, it was found that the difference was statistically significant ($p<0.001$) and not due to the treatment (Table 3).

Discussion

In this study pupil cycle time of the healthy control group was determined to be 820 (SD 47) ms. Lepore and coworkers¹² reported the PCT of a control group as 801.9 (SEM 8.9) ms. Miller and Thompson¹¹ measured PCT of a control group as 822 (69) ms (mean and SD), and Campbell and Whiteside¹³ as 870 (170) ms. In the present study the PCT difference between the eyes of the subjects from the control group was measured as 30 (13) ms whereas Miller and Thompson reported the PCT difference between the eyes as 30 (36) ms.¹¹

In all three leprosy groups included in this study the PCT was higher than in the control group. Moreover, the PCT of the leprosy patients without any intraocular involvement was higher than in the control group. These results show that in the ophthalmic examination of leprosy patients without any symptoms such as keratic precipitates, posterior synechiae, sequelae of posterior synechiae, iris atrophy, iris pearl, etc., the fact that the autonomic nerve system of the eye suffers from the leprosy can often be determined by measuring the PCT.

An affected autonomic nerve system indicates the presence of *Mycobacterium leprae* in the eye. After the bacillus reaches the eye uveitic reactions will start, which may lead to blindness. Malaty and coworkers¹⁴ studied 70 nine-banded armadillos with leprosy and found that involvement of the ciliary body was 96%, conjunctiva 68%, iris 64%, cornea 44%, and choroidea 30%.

Table 4 Comparison of the mean differences between cycle times of the fast and slow eye of a pair

	Mean difference between cycle times of the fast and slow eye of a pair (SD) ms		
Disease groups	Healthy controls (n=25)	p	
Lepromatous leprosy n=17	94 (63)	30 (13)	<0.001
Borderline lepromatous leprosy n=18	70 (60)	30 (13)	<0.001
Borderline tuberculoid leprosy n=5	83 (66)	30 (13)	<0.001
Pulmonary tuberculosis n=10	40 (12)	30 (13)	>0.05
Duhning disease n=8	36 (11)	30 (13)	>0.05

Leprosy causes various degrees of post-ganglionic autonomic denervation. Using this fact Swift and Bauchard¹⁰ tried to detect autonomic denervation hypersensitivity among leprosy patients. They showed the presence of denervation hypersensitivity using L-epinephrine 0.1% in 11 of the 20 leprosy patients. They reported that there was no obvious symptom for the 11 subjects with hypersensitivity; and 8 of the 9 subjects without any hypersensitivity showed symptoms of eye involvement. In other words, Swift and Bauchard found very few patients without any eye involvement as a result of leprosy. The fact that there was no denervation hypersensitivity among leprosy patients with eye involvement can be explained by difficulty of penetration of L-epinephrine through the intact cornea. The photographic determination of autonomic denervation hypersensitivity using L-epinephrine drops is a difficult method which requires large groups of subjects and extreme care in application.

The PCT therefore offers simple, fast, quantitative measurements with a high degree of repeatability. And since the PCT can be measured at regular intervals it will probably give information about the autonomic nervous system and integrity of the iris along with a warning about the uveitic reactions. An increased

PCT distinguishes the patients with intraocular involvement from the rest of the group. In this way ophthalmologists can perform more frequent examinations of patients at risk and avert complications resulting from the insidious uveitic reactions.

- 1 Pfaltzgraff RE, Bryceson A. Clinical leprosy. In: Hastings RC, ed. *Leprosy*. Churchill-Livingstone, Edinburgh, London, Melbourne, New York, 1985: 134-75.
- 2 Jopling WH. *Handbook of leprosy*. 2nd ed. London: Heinemann, 1978: 1-5, 66-74.
- 3 Noorden SK. The epidemiology of leprosy. In: Hastings RC, ed. *Leprosy*. Churchill-Livingstone, Edinburgh, London, Melbourne, New York, 1985: 15-30.
- 4 Courtright P, Johnson GJ. *Prevention of blindness in leprosy*. London: International Centre for Eye Health, 1988: viii.
- 5 Binford CH, Meyers WM, Walsh GP. Leprosy. *JAMA*. 1982; 247: 2283-92.
- 6 Ridley DS, Jopling WH. Classification of leprosy according to immunity: a five-group system. *Int J Lepr Other Mycobact Dis* 1966; 34: 255-73.
- 7 Courtright P. Defining the magnitude of ocular complications from leprosy: problems of methodology. *Int J Lepr Other Mycobact Dis* 1988; 56: 566-73.
- 8 Brand MB. Care of the eye in Hansen's disease. 2nd ed., Carville LA: The Star, 1987: 3-14.
- 9 ffytche TJ. Role of iris changes as a cause of blindness in lepromatous leprosy. *Br J Ophthalmol* 1981; 65: 231-9.
- 10 Swift TR, Bauchard FD. Pupillary reactions in lepromatous leprosy. *Int J Lepr Other Mycobact Dis* 1972; 40: 142-8.
- 11 Miller SD, Thompson HS. Edge-light pupil cycle time. *Br J Ophthalmol* 1978; 62: 495-500.
- 12 Lepore RE, Sanborn GE, Slevin JT. Pupillary dysfunction in myasthenia gravis. *Ann Neurol* 1979; 6: 29-33.
- 13 Campbell FW, Whiteside TCD. Induced pupillary oscillations. *Br J Ophthalmol* 1960; 34: 180-9.
- 14 Malaty R, Walsh GP, Meyers WM, Binford CH, Job CK. Ocular leprosy in nine-banded armadillos. *Invest Ophthalmol Vis Sci* 1986; 27 (suppl 38).

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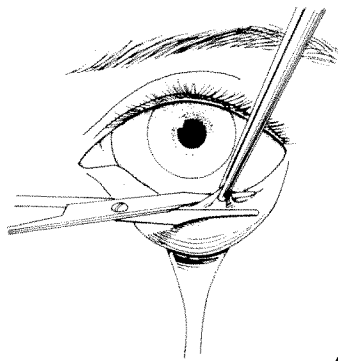
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K. N. Leibovic, State University of New York, Buffalo (Ed.)

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J. A. Mauriello, University of New Jersey; **J. C. Flanagan**, University of Philadelphia, PA (Eds.)

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K. Lucke, H. Laqua, University of Lübeck

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M. Bonnet, University of Lyon

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B. R. Masters, Georgia Institute of Technology (Ed.)

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Foreword by D. Maurice

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M. P. Nadler, Sewickley, PA; **D. Miller**, Boston, MA; **D. J. Nadler**, University of Pittsburgh, PA (Eds.)

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G. K. Klintworth, Duke University, Durham, NC

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T. Brandt, University of Munich

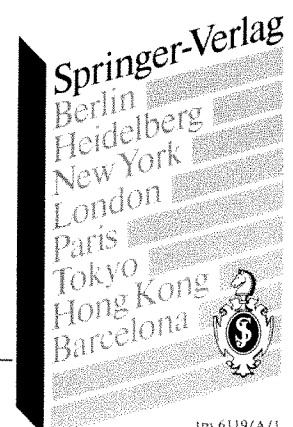
Vertigo

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Electrophysiology and colour perimetry in dominant infantile optic atrophy

T A Berninger, W Jaeger, H Krastel

Abstract

A typical finding in dominant infantile optic atrophy (DIOA) is the variation of the phenotypic expression of the DIOA gene even within one family. It is of special interest for genetic consultation to evaluate an examination method for detecting subclinically involved patients. Seven patients of two families were examined. Three of them had the typical symptoms of DIOA: reduced visual acuity, tritan defect, temporal pallor of both optic discs, and a relative central scotoma for white test spots. In visual evoked cortical potentials (VECP) the amplitudes were reduced, and in one patient the latencies were slightly delayed and two patients considerably so. The amplitude of the negative component of the PERG was markedly reduced, while the positive component was normal. In the remaining four family members normal retinal and cortical responses were recorded under standard conditions and visual fields and colour vision (FM 100 hue) were also normal. However, static perimetry with blue test spots showed in two family members enlarged central scotomas, thus proving that they had subclinical DIOA.

A tritan defect forms the decisive diagnostic clue to most cases of dominant infantile optic atrophy (DIOA).¹⁻⁴ François⁵ and Verriest⁶ found that the colour arrangement tests are particularly suitable for discovering such acquired tritan defects. In particular the desaturated Panel D15 has proved to be successful in the early detection of tritan defects in dominant optic atrophy.⁷

These findings are inconsistent with Koellner's rule that lesions of the receptor and bipolar retinal layers cause loss of blue-yellow sensitivity and that lesions of the ganglion cells and pre-geniculate pathways affect red-green.⁸ Histological findings, however, identified the retinal ganglion cells as the site of primary damage in DIOA.⁹⁻¹⁰ Further, it is striking that the phenotypic expression of the DIOA gene varies even within a family,¹¹⁻¹³ ranging from severely affected patients who have both red-green and blue-yellow defects^{7,14} to those scarcely affected in whom not even a tritan defect can be observed. Visual fields tested in the usual clinical manner frequently show only mild abnormalities or at times appear normal.¹⁵ Even the optic nerve may show only questionable pallor or appear normal in some individuals.¹² Krill *et al*¹² therefore recommended that an experienced ophthalmologist should examine the optic nerve head so that subtle changes might also be detected.

The aim of this study was the evaluation of methods for detecting subclinical involved patients with DIOA.

Patients and methods

Two families (family A: five members; family B: two members) were examined. We recorded the best corrected visual acuity and the results of slit-lamp biomicroscopy, Tübinger automatic perimetry (TAP) (family A), the Goldmann visual field test (family B), the Farnsworth-Munsell 100-hue test (A2, A3, A4, A5), the Panel D-15 desaturated test (A1, B1, B2), funduscopy, pattern reversal evoked cortical potentials (VECP), and pattern reversal electroretinogram (PERG) tests.

VISUAL EVOKED CORTICAL POTENTIALS (VECP)

The standard conditions for the VECP were as follows: Checkerboard pattern stimuli were generated on a black-and-white TV monitor. The field size of the screen subtended 14.5° by 18.5° and the checks were 38 min of arc. The mean luminance was 30 cd/m² and the modulation depth was 0.97. The checks were temporally alternated at a modulation rate of four reversals/s (2 Hz). The active electrode was attached 2-3 cm above the inion. The right ear was earthed and the reference electrode fixed to the left ear. All VECP recordings were monocular. In some cases the mean luminance was reduced to 10 cd/m² and the modulation depth to 0.2 (reduced contrast test).

PATTERN ELECTRORETINOGRAM (PERG)

Arden gold foil electrodes were used.¹⁶ The reference electrode was placed on the ipsilateral temple, thus minimising retinal and cortical contamination.^{17,18} The stimulus was provided by a checkerboard pattern reversal on a TV screen of 14.5° by 18.5°. The visual angle of each square was 50 min of arc, modulation depth 0.97, reversing rate 4 rev/s (2 Hz).

Retinal and cortical potentials were amplified by a Medelec AA6 with bandpass setting 0.16 and 32 Hz and averaged by a Nicolet 1170. Four samples of 64 sweeps were used to obtain the final result.

COLOUR VISUAL FIELD

With the Tübinger automatic perimeter (TAP)¹⁹ white and blue test spots of 0.16° diameter were presented for 200 ms. Yellow adaptation (Schott OG 530 nm cutoff filter) was applied to isolate the activity of the blue system. Luminance distribution was adjusted to compensate for the loss of sensitivity towards the periphery (for details see Krastel *et al*²⁰). A small foveal scotoma was obtained for normal subjects using blue test spots, which is due to the foveal tritanopia.²¹

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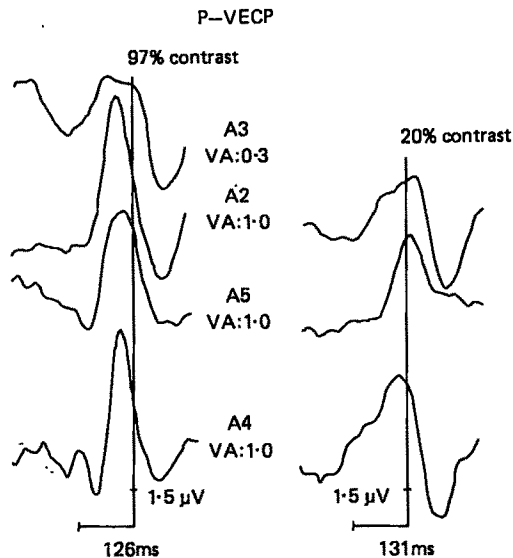
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Figure 1 Visual evoked cortical potentials are shown. On the left are the recordings with high contrast and on the right those with low contrast. Note that for high contrast all three family members of patient (A3) have a normal VECP (A2, A4, A5), while for low contrast two patients (A2, A5) have a slightly increased P100 latency above 2 SD.



COLOUR VISION

Colour vision was tested by Farnsworth-Munsell 100-hue, Panel D-15 desaturated test, tritanomaloscopy, and spectral increment thresholds.

Results

VISUAL EVOKED CORTICAL POTENTIALS

The visual evoked potentials were only abnormal in the severely affected patient (A3, B1, B2) (Fig 1). In B1 and B2 a positive-negative-positive (PNP) complex was observed. In contrast, patient A3 had a broad positive deflection with only a slight delay of the P-100 latency.

PATTERN ELECTRORETINOGRAM

PERGs were obtained in all patients. Normal positive components were measured in all seven patients. The negative components of the patients A1, A2, A4, and A5 were also in the normal range. However, a significantly reduced negative component was found in three other patients (A3, B1, B2) with definite DIOA.

COLOUR VISUAL FIELD

The visual fields of both members of family B were tested with a Goldmann perimeter. A central scotoma was found in both patients. All

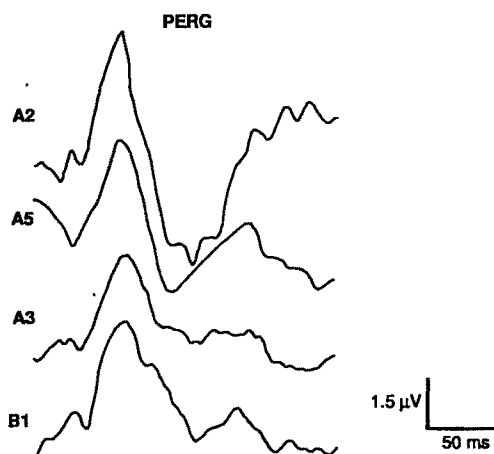


Figure 2 Pattern electroretinograms of four patients (A2, A3, A5, B1) are shown. Note that the two subclinically involved patients (A2, A5) have normal positive and negative PERG components, while hardly any negative PERG component was recorded for the severely affected patients (A3, B1).

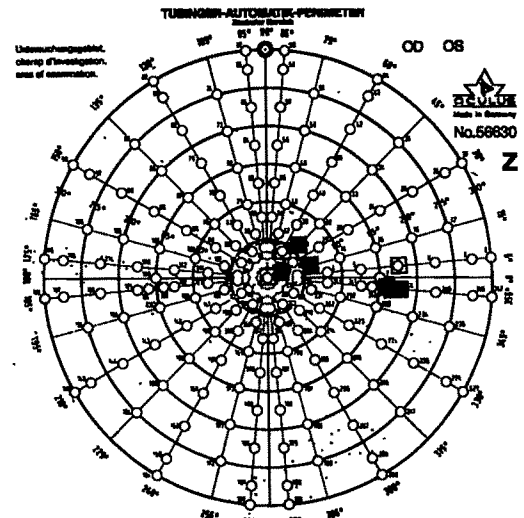


Figure 3 Normal static perimetry fields for white test spots is shown for patient (A5).

members of family A were tested with the TAP. With the white test spot a central scotoma was observed only in patient A3. His father (A1) and his eldest sister (A4) also had a normal visual field for blue test spots, but the mother (A2) and the younger sister (A5) both had an enlarged central scotoma (Figs 3 and 4).

COLOUR VISION

Four patients (A2, A3, A4, A5) were tested with the Farnsworth Munsell 100-hue test and three (A1, B1, B2) with the Panel D-15. Colour arrangement tests detected an obvious defect only in those patients (A3, B1, B2) who showed significant signs of the disease. However, we observed one obligate and one possible carrier of the gene, who according to the conventional tests (visual acuity, colour arrangement, white perimetry) seemed to be not involved. For reasons of colour perimetry (see Discussion) we regarded these patients (A2, A5) as subclinically affected. The results of the tritanomaloscopy and spectral sensitivity are published elsewhere.²²

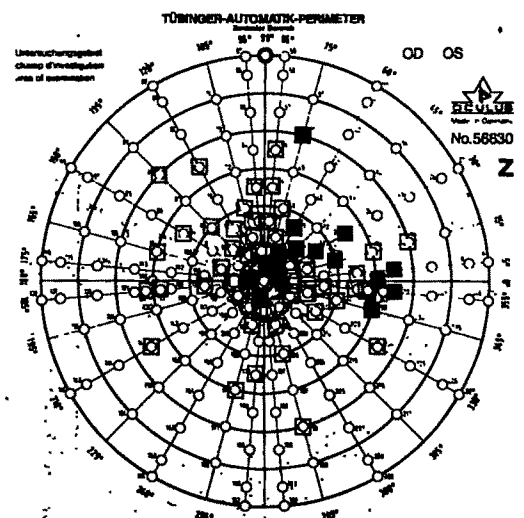


Figure 4 Static perimetry field for blue test spots is shown for patient (A5). A large central scotoma is present, while the visual field for white test spots was normal (see Fig 3).

Table 1 Patients examined by static perimetry and blue test targets

Pat.	Sex	Age	VA		Optic disc	F-100	Perimetry	
			RE	LE			White	Blue
A1	M	74 yr	1.0	1.0	Normal	D-15 Normal	Normal	Normal
A2	F	65 yr	1.0	0.8	?Temp. pallor	118 (-180)	Normal	CS
A3	M	37 yr	0.3	0.3	Temp. pallor	504 (-108)	CS	CS
A4	F	34 yr	1.0	1.0	Normal	24 (-108)	Normal	Normal
A5	F	30 yr	1.0	1.0	?Temp. pallor	88 (-92)	CS	CS
B1	M	42 yr	0.2p	0.2p	Temp. pallor	Tritan	CS	—
B2	M	18 yr	0.3p	0.3p	Temp. pallor	Tritan	CS	—

VA=Visual acuity. CS=central scotoma. ?Temp. pallor=questionable temporal pallor.

Discussion

The aim of this study was to find a diagnostic clue for detecting subclinical involvement in DIOA. We first studied severely affected patients to determine the precise changes in patients with DIOA.

VISUAL EVOKED CORTICAL POTENTIALS

Harding *et al*²³ and Crews and Harding²⁴ observed a positive-negative-positive (PNP) response (negativity around 100 ms) in most patients with DIOA. The characteristic PNP complex was more commonly seen with flash stimuli. It is not yet clear whether this triphasic PNP response is generated by a negative replacement of the positive P100 (P2) component. We recorded the flash VECF only in one patient (B1) and did not find the PNP complex. However, using pattern reversal stimuli we observed the PNP complex in two patients (B1, B2), while in one patient (A3) a broad deflection with only a slight delay was found. The broad envelope of the response suggests that, while some neural elements have more or less retained their function, others are more seriously affected. It should be remarked that the visual acuity was more impaired in the patients (B1, B2) in whom the amplitudes of VECF were more reduced and the PNP complex appeared. In patients with more severe visual impairment Kline and Glaser²⁵ recorded diminished amplitudes and prolonged latencies, consistent with neural conduction defects. These observations support the idea that the PNP complex might be a marked delay of the P100 components of the VECF. A follow-up study may evaluate whether all our patients develop a PNP in parallel with their decreasing visual acuity. However, it has to be noted that the recording technique of Harding *et al*²³ and Crews and Harding²⁴ is different from ours and that of Kline and Glaser,²⁵ which may also explain the different findings.

It is believed that in DIOA contrast processing is particularly affected.²⁶ Since we observed normal P100 latency in all four family members using high modulation depth (0.97), we reduced the modulation depth to 0.2 and the mean luminance to 10 cd/m². We expected that this stimulus would be close to the threshold of the slightly altered ganglion cells of the patients subclinically involved. However, the delay seen in two patients (A2, A5) was between 2 and 3 standard deviations of a normal mean value (Fig 1).

PATTERN ELECTRORETINOGRAM

The PERG has at least two components: an early

positive component which is not specific to changes in retinal distribution of contrast, followed by a negative wave showing spatial tuning across temporal frequency.²⁷ Recently Holder²⁸ observed that the positive component of the PERG is reduced in macula diseases while in optic nerve disease the negative component of the PERG is selectively decreased, and this has been confirmed.²⁹ DIOA is a clear-cut case of damage confined to the optic nerve, and our findings in the patients A3, B1, and B2 thus strengthen the claim that the negative PERG component is affected in optic nerve defects. Papst *et al*³⁰ observed a normal positive component of the PERG in their patients, as we did in cases (A3, B1, B2). However, again normal results were obtained for our subclinically involved family members (Fig. 2).

COLOUR VISUAL FIELD

Testing the visual field with a coloured target is not a new method. A paradoxical phenomenon has been observed in DIOA patients in kinetic perimetry: since the perception for blue targets is poorer than for red targets, the red field is larger than the blue (red-blue inversion).³¹⁻³⁷ Static perimetry, however, is more sensitive than kinetic perimetry for detecting small field defects and relative scotomas.^{4 17 20 38}

Therefore we examined the patients by static perimetry and blue test targets, thus obtaining a much higher sensitivity of the visual field test. We could then detect a central scotoma for blue test targets in subclinically involved patients (A2, A5), while visual acuity, FM 100-hue, and visual field tests for white targets are still normal (Table 1).

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- Jaeger W. Dominant vererbte Optikusatrophie (unter besonderer Berücksichtigung der dabei vorhandenen Farbsinnstörungen). *Graefes Arch Clin Exp Ophthalmol* 1954; 155: 457-84.
- Lodberg CV, Lund A. Hereditary optic atrophy with dominant transmission. Three Danish families. *Acta Ophthalmol (Kbh)* 1950; 28: 437-49.
- Kjer P. Congenital optic atrophy with dominant mode of inheritance: a clinical and genetic study of 19 Danish families. *Acta Ophthalmol (Kbh)* 1959; 37 (suppl): 54-145.
- Grützner P. Über Diagnose und Funktionsstörungen bei der infantilen dominant vererbten Optikusatrophie. *Ber Dtsch Ophthalmol Ges* 1963; 65: 268-73.
- François J. An acquired deficiency of colour vision. *Vision Res* 1961; 1: 201-19.
- Verriest G. Further studies on acquired deficiency of color discrimination. *J Opt Soc Am* 1963; 53: 185-95.
- Jaeger W, Boerner C, Boerner C. Verlaufsbeobachtungen der Farbsinnstörung (Tritandefekt) bei dominanter infantiler Optikusatrophie. In: Herzau von, ed. *Pathophysiologie des Sehens*. Stuttgart: Enke, 1984: 87-95.
- Koellner H. Die Störung des Farbsinnes, ihre Bedeutung und ihre Diagnose. Berlin: Karger, 1912.
- Johnston PB, Gaster RN, Smith VC, Tripathi RC. A clinicopathological study of autosomal dominant optic atrophy. *Am J Ophthalmol* 1979; 88: 868-75.
- Kjer P, Jensen OA, Klinken L. Histopathology of eye, optic nerve and brain in a case of dominant optic atrophy. *Acta Ophthalmol (Kbh)* 1983; 61: 300-12.
- Grützner P. Über erworbene Farbsinnstörungen bei Sehnervenerkrankungen. *Graefes Arch Clin Exp Ophthalmol* 1966; 169: 366-84.
- Krill AE, Smith VC, Pokorny J. Similarities between congenital tritan defects and dominant optic-nerve atrophy: coincidence or identity? *J Opt Soc Am* 1970; 60: 1132-9.
- Jaeger W. Dominant hereditary optic atrophy and Leber's disease. *Doc Ophthalmol Proc Ser* 1978; 17: 91-115.
- Krill AE, Smith VC, Pokorny J. Further studies supporting the identity of congenital tritanopia and hereditary dominant optic atrophy. *Invest Ophthalmol Vis Sci* 1971; 10: 457-65.

- 15 Smith DP. Diagnostic criteria in dominantly inherited juvenile optic atrophy: a report of three new families. *Am J Optom Physiol Opt* 1977; 49: 183-200.
- 16 Arden GB, Carter RM, Hogg CR, Siegel IM, Margolis S. A gold foil electrode: extending the horizons for clinical electroretinography. *Invest Ophthalmol Vis Sci* 1979; 18: 421-6.
- 17 Hess RF, Baker CL. Human pattern-evoked electroretinogram. *J Neurophysiol* 1984; 51: 939-51.
- 18 Berninger TA. The pattern electroretinogram and its contamination. *Clin Vision Sci* 1986; 1: 185-90.
- 19 Aulhorn E, Durst W. Rasterperimetrie in der augenärztlichen Praxis. *Fortschr Ophthalmol* 1982; 79: 350-3.
- 20 Krastel H, Jaeger W, Braun S. Rasterperimetrie mit Farbzeilen. *Fortschr Ophthalmol* 1986; 83: 690-701.
- 21 Williams DR, MacLeod DIA, Hayhoe MM. Foveal tritanopia. *Vision Res* 1981; 21: 1341-75.
- 22 Jaeger W, Berninger TA, Krastel H. Pathophysiological considerations in dominant optic atrophy based upon spectral sensitivity, tritanomaloscopy, blue perimetry and visual electrophysiology. In: Verriest G, ed. *Colour vision deficiencies VIII*. Dordrecht: Martinus Nijhoff/Dr W Junk, 1987: 397-411.
- 23 Harding GFA, Crews SJ, Pitts M. Psychophysical and visual evoked potential findings in hereditary optic atrophy. *Trans Ophthalmol Soc UK* 1979; 99: 96-102.
- 24 Crews SJ, Harding GFA. Visual evoked potentials and psychophysical findings in dominant hereditary optic atrophy. *Doc Ophthalmol Proc Ser* 1981; 27: 167-74.
- 25 Kline LB, Glaser JS. Dominant optic atrophy: the clinical profile. *Arch Ophthalmol* 1979; 97: 1680-6.
- 26 Jaeger W, Krastel H. Degenerative Erkrankungen des Nervus opticus. In: Lund OB, Waubke TN, eds. *Degenerative Erkrankungen des Auges*. Stuttgart: Enke, 1983: 151-60.
- 27 Berninger TA, Schuurmans RP. Spatial tuning of the pattern ERG across temporal frequency. *Doc Ophthalmol* 1985; 61: 17-25.
- 28 Holder GE. Significance of abnormal pattern electroretinography in anterior visual pathways dysfunction. *Br J Ophthalmol* 1987; 71: 166-71.
- 29 Ryan S, Arden GB. Electrophysiological discrimination between retinal and optic nerve disorder. *Doc Ophthalmol* 1988; 68: 247-55.
- 30 Papst N, Bopp M, Wundrack EM. Muster-ERG und Muster-VECP bei autosomal dominanter infantiler Optikusatrophie. *Fortschr Ophthalmol* 1985; 82: 300-1.
- 31 Scott JG. Hereditary optic atrophy with dominant transmission and early onset. *Br J Ophthalmol* 1941; 25: 461-79.
- 32 Iverson HA. Hereditary optic atrophy. *Arch Ophthalmol* 1958; 59: 850-3.
- 33 Ruby J, Davey JB. Dominantly inherited optic atrophy. *Br J Ophthalmol* 1958; 42: 413-24.
- 34 Grehn F, Kommerell G, Ropers HH, Giesing B. Dominant optic atrophy with sensorineural hearing loss. *Ophthalmic Paediatr Genet* 1982; 1: 77-88.
- 35 Ohba N, Inamura PM, Tanino T. Colour vision in a pedigree with autosomal dominant optic atrophy. *Mod Probl Ophthalmol* 1976; 17: 315-9.
- 36 Caldwell JBH, Howard RO, Riggs LA. Dominant juvenile optic atrophy: a study in two families and review of hereditary disease in childhood. *Arch Ophthalmol* 1971; 85: 133-47.
- 37 Hoyt CS. Autosomal dominant optic atrophy: a spectrum of disability. *Ophthalmology* 1980; 87: 245-51.
- 38 Verriest G. Further studies on acquired deficiency of colour vision. *J Opt Soc Am* 1963; 53: 185-95.

MINI REVIEW

Subretinal membranes of proliferative vitreoretinopathy

Subretinal membranes (SRMs), also known as retroretinal bands or membranes, are a well recognised complication of rhegmatogenous retinal detachment and as such are part of the spectrum of proliferative vitreoretinopathy (PVR).¹ Proliferative vitreoretinopathy SRMs are of two main types. The majority tend to form diffuse cell sheets which do not interfere with retinal attachment and over which, in the absence of contractile epiretinal proliferation, the retina may be reattached with scleral buckling procedures alone.² The second group of PVR SRMs embodies taut membranes or bands (often in an annular configuration) which raise the neuroretina and impede conventional retinal detachment surgery. This second, problematic type of SRM occurs in 13% of patients with PVR³ and usually requires microsurgical division. An internal approach to tensile SRMs, such as described by Machemer in 1980,⁴ may enable retinal reapposition and, incidentally, provide specimens for research.

Laboratory investigations provide some information on the pathobiology of proliferative vitreoretinopathy SRMs. Subretinal membranes in PVR are cellular or fibrocellular in composition and most are avascular. Diffuse sheets of subretinal cells which do not obstruct retinal apposition ('simple SRMs') are usually glial and contain little or no extracellular material. By contrast taut SRMs are fibrocellular, and up to 95% of the cells are retinal pigment epithelial in origin, while the extracellular component includes fibrin and collagen types I to IV.

Of particular interest is the source of the tension in problematic subretinal membranes. Since the SRMs do not appear to contain elastin, it is thought that the traction is generated by contractile retinal pigment epithelial cells with some characteristics of myofibroblasts.⁵ However, myofibro-

blast-like cells are not always present in tensile SRMs, though the absence of such cells might relate to delayed removal of the membranes.⁶ Nevertheless SRMs probably develop over many months, and so the absence of myofibroblastic cells in some specimens is mysterious if such cells are the origin of the traction.

Whatever the mechanism(s) of the tension in subretinal membranes in cases of PVR, there is no pharmacological means to counter it in vivo, and therefore the management of patients with problematic SRMs relies on vitreoretinal surgery. However, when a surgical approach to SRMs is required, the visual outcome is frequently disappointing, with only a 20% chance of a restoration of ambulatory vision.³ Thus the prevention of PVR membrane formation, by a combination of early surgical and drug intervention in retinal detachment,⁷ is an important research avenue in which carefully planned antiproliferative drug regimens may come to have a major role.

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- 1 Retina society terminology committee. The classification of retinal detachment with proliferative vitreoretinopathy. *Ophthalmology* 1983; 90: 121-5.
- 2 Machemer R. Discussion of presentation by Federman JL, Foldberg R, Ridley M, and Arbizo VA. Subretinal cellular bands. *Trans Am Ophthalmol Soc* 1983; 81: 172-80.
- 3 Lewis H, Aaberg TM, Abrams GW, McDonald HR, Williams GA, Mieler WF. Subretinal membranes in proliferative vitreoretinopathy. *Ophthalmology* 1989; 96: 1403-15.
- 4 Machemer R. Surgical approaches to subretinal strands. *Am J Ophthalmol* 1980; 90: 81-5.
- 5 Trese MT, Chandler DB, Machemer R. Subretinal strands: ultrastructural features. *Graefes Arch Clin Exp Ophthalmol* 1985; 23: 35-40.
- 6 Wilkes SR, Mansour AM, Green WR. Proliferative vitreoretinopathy histopathology of retroretinal membranes. *Retina* 1987; 7: 94-101.
- 7 Scott JD. Prevention and perspective in retinal detachment. *Eye* 1989; 3: 491-515.

CASE REPORTS

Post-traumatic hyperlipofuscinosis in the human retinal pigment epithelium

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Abstract

Light microscopy (including fluorescence microscopy) and electron microscopy were applied to a study of the photoreceptor-retinal pigment epithelium (RPE) complex in a human eye which had been severely traumatised nine months prior to enucleation. The main feature of interest was a massive accumulation of lipofuscin in the retinal pigment epithelium at the posterior pole, and quantitative fluorescence microscopy provided values three times those obtained in appropriate control tissue. The photoreceptor layer was normal at the posterior pole but became progressively atrophic towards the periphery. The concentration of lipofuscin was proportional to the degree of preservation of the retinal photoreceptors. By electron microscopy the cells in the RPE were seen to be packed with a mixture of lipofuscin granules and melanolysosomal complexes, but occasional photoreceptor phagosomes were found. Bruch's membrane and the choriocapillaris were normal. We attribute this hitherto unreported abnormality of the RPE after trauma to a dysfunction consequent on an overload of the monolayer by photoreceptor debris at the time of trauma.

deposition of lipofuscin in the RPE in a traumatised eye which was submitted for routine examination. Since this complication of trauma has not to our knowledge been reported previously, we performed a morphological study to promote further understanding of the effects of overload of the RPE phagocytic systems by excessive photoreceptor disc material.

Materials and methods

CLINICAL HISTORY

A 55-year-old male was seriously injured in a fight in February 1982. He sustained a fractured skull and a fractured mandible, with severe contusion of the left orbit. A scleral rupture in the left eye was not noted until the orbital effusion had settled, and when first seen by an ophthalmologist the sclera had healed and intervention was not required. The patient failed to attend hospital until November 1982, when he returned complaining of severe pain. On examination the eye was disorganised and blind, and enucleation was performed on 24 November, some nine months after the injury. In the ensuing years the right eye has been normal.

It is now accepted that there is constant renewal of photoreceptor outer segments and that groups of discs, bound within a membrane, are released from the photoreceptor tips and are phagocytosed and degraded by the cells of the retinal pigment epithelium (RPE).^{1,2} The biochemical processes which are involved in the enzymatic dissolution of the photoreceptor phospholipid are less well understood, but in the normal cell it seems likely that the end stage of a photoreceptor disc phagosome is a residual body.^{1,2} Morphological studies have shown that the number of lipofuscin granules increases with age in the RPE, particularly at the posterior pole,^{3,7} and the assumption is that this represents a dysfunction in the degradative mechanisms required for disc lipoprotein phagocytosis, though the autophagic destruction of mitochondrial membranes probably makes a contribution.^{4,6} Reports describing excessive amounts of lipofuscin in the RPE are rare and are limited, to a 'choroidal dystrophy',⁴ a case of retinitis pigmentosa,⁸ a carrier in chorioceraemia,⁹ and to ceroid lipofuscinosis in the human eye,¹⁰ and in animal tissues.¹¹

It was therefore surprising to find a massive

PATHOLOGY

The globe was fixed in 4% glutaraldehyde in 0.1 M cacodylate buffer and measured 23×22.5×23 mm; the optic nerve was cut flush. The central part of the enucleated eye was embedded in paraffin wax and studied by serial section and conventional special stains which included periodic acid Schiff (PAS), Prussian blue, Bodian, and Loyez. Unstained sections were mounted in fluorescence-free mounting medium and examined in ultraviolet light (Leitz Pleomepi illumination system with excitation at 380-400 nm and transmission at 460-480 nm). For quantitative studies of the lipofuscin content of the pigment epithelium the UV fluorescence microscope was attached to an image analyser (Optomax System I; Micromasurements Ltd, Cambridge). Control tissue from cases in which the RPE-photoreceptor complex was normal were used to obtain a baseline for comparison with the traumatised eye (Table 1), and for interest the analysis was also performed on an eye containing a metastatic tumour with partial exudative detachment and an eye which had siderosis bulbi (Table 1) to assess the respective

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Table 1 Area of lipofuscin (μm^2) in a 50 μm length of RPE

Age	Sex	Diagnosis	Area of lipofuscin, Mean (SD)	Nos of measurements
<i>Control tissue</i>				
(a) 19	M	Iris melanoma	50 (25)	50
(b) 73	F	Acute glaucoma	250 (50)	25
<i>Relevant pathology</i>				
(c) 53	F	Metastatic breast carcinoma	175 (75)	25
		Retina in situ	150 (50)	25
(d) 46	M	Exudative detachment		
		Intraocular foreign body	8 (8)	25
		Siderotic RPE	225 (100)	25
		Non-siderotic RPE		
55	M	Post-traumatic hyperlipofuscinosis	600 (170)	50

effects of retinal detachment and iron accumulation on the lipofuscin content. The sections were treated in an identical manner in terms of anatomical sampling for the measurement of lipofuscin. The measurements were expressed as the area of lipofuscin autofluorescence (μm^2) per 50 μm length of pigment epithelium.

Six blocks from the retina of the traumatised eye were postfixed with osmium tetroxide and processed through Araldite for electron microscopic study by a Philips 301 microscope. Two blocks from the regions of good photoreceptor preservation were not treated with osmium, so that lipofuscin and melanin granules in the RPE could be more easily differentiated.

Results

ROUTINE PATHOLOGICAL EXAMINATION

Macroscopic examination. The cornea was opaque and fibrotic, but transillumination revealed a superior iris defect, and the globe was opened in the vertical plane. The anterior chamber was narrowed by iridocorneal contact, and the globe was aphakic. Scar tissue replaced the superior parts of the iris and ciliary body, and vitreous traction folds were present at the retinal periphery; the posterior retina was in situ, but had a slate grey appearance. The mid periphery of the

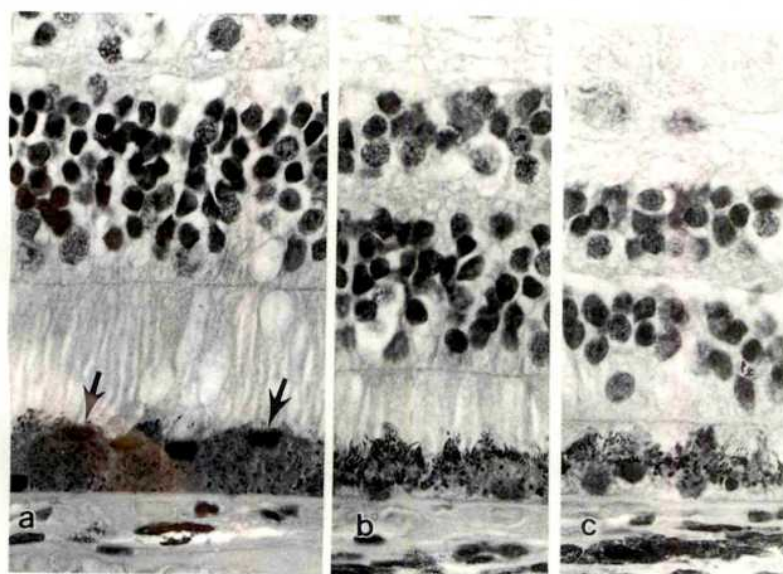


Figure 1 The light microscopic appearance of the outer retina at (a) the posterior pole, (b) the mid periphery, and (c) toward the equator. Note the progressive atrophy of the photoreceptors in height and number and the loss of nuclei in the outer nuclear layer. In (a) the retinal pigment epithelial cells are enlarged by an accumulation of lipofuscin in the cytoplasm and there is internal displacement of some nuclei (arrows). Bruch's membrane and the choriocapillaris are normal. (Haematoxylin-eosin, $\times 475$.)

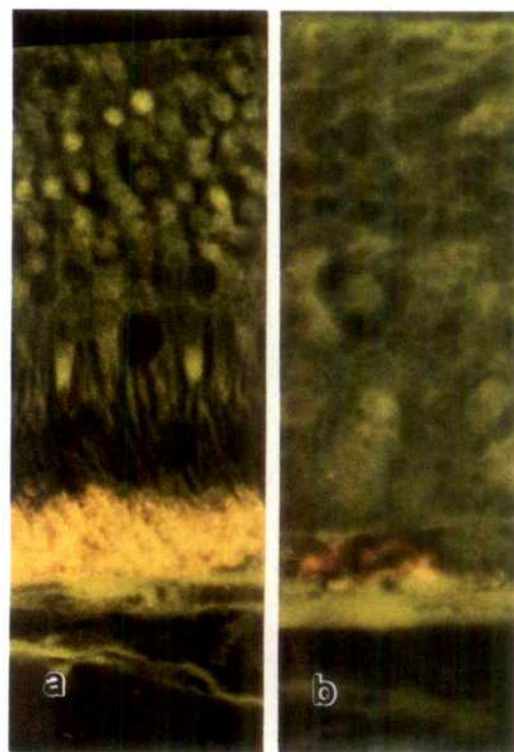


Figure 2 In ultraviolet light, the autofluorescence of lipofuscin granules is striking in the RPE at the posterior pole (a), by comparison with the equator (b). ($\times 630$.)

retina showed a fine granular pigmentary disturbance with an almost linear series of small brown particles arranged in the coronal plane. A few hyalinised white vessels contained pigment granules in the walls, but the appearance was unlike that seen in post-traumatic pseudoretinitis pigmentosa. The macula was swollen by oedema, and the peripapillary retina was thickened by a small extrusion of myelin due to crushing of the optic nerve by a snare (toothpaste artefact).

Paraffin histology. The corneal pathology included stromal fibrosis, and the anterior segment was distorted by a fibrous ingrowth from the healed wound at the superior limbus; this ingrowth extended to the inferior iris leaf. Lens remnants were identified in the corneal wound, from which a fibrous band extended into the vitreous. This fibrous band contained haemomacrophages and had drawn the superior peripheral retina across the pars plana. Below, the inner leaf of a retinoschisis was drawn across the pars plana by vitreous traction. The uveal tract contained an inconspicuous lymphoplasmacytoid infiltrate.

Apart from a mild and sparse lymphocytic perivasculitis, the architecture of the inner two-thirds of the retina was preserved. The following abnormalities were observed in the outer retina:

At the posterior pole there was cystoid macular oedema and a small exudative detachment beneath the fovea, but the perifoveolar photoreceptors were of normal architecture (Fig 1a). The RPE adjacent to the normal photoreceptors was swollen by accumulations of PAS-positive granules, which in some cells displaced the nuclei to the inner aspect (Fig 1a). The lipofuscin content was high (Fig 2a), and the iron stain was negative in the RPE in this region.

Toward the midperiphery the inner and outer segments of the photoreceptors were shorter (Fig 1b). The lipofuscin content of the RPE cells was lower in this location.

Toward the equator the atrophy of the outer retina was more pronounced (Fig 1c). At the equator the retinal pigment epithelium was flattened and atrophic, and clumps of pigment laden cells were present within the retina. The RPE and the cells within the retina stained positively for iron, but the ipofuscin content was markedly reduced in the RPE (Fig 2b).

QUANTITATIVE ANALYSIS OF LIPOFUSCIN CONTENT
Values obtained for measurement of lipofuscin in the RPE in various specimens are shown in Table 1.

In the control specimens in which the posterior RPE and retina were of normal appear-

ance there was a five-fold difference in the area of fluorescent material when values from the 19-year-old (50, SD 25) and the 73-year-old (250, SD 50) were compared. There was considerable variation round the mean in the younger eye and a more uniform distribution in the older eye. The values obtained for lipofuscin in the RPE in the eye of a 53-year-old female with an isolated metastatic tumour were of a similar order irrespective of attachment (175, SD 75) or detachment (150, SD 50) of the retina. In the traumatised globe from a 46-year-old male in which intense iron deposition was observed in the RPE adjacent to an iron-containing foreign body, values for lipofuscin were remarkably low in the presence of iron (8, SD 8), but were within the range provided by the other comparison specimens where iron staining was absent (225, SD 100). Values obtained for the lipofuscin content of the RPE at the posterior pole in the

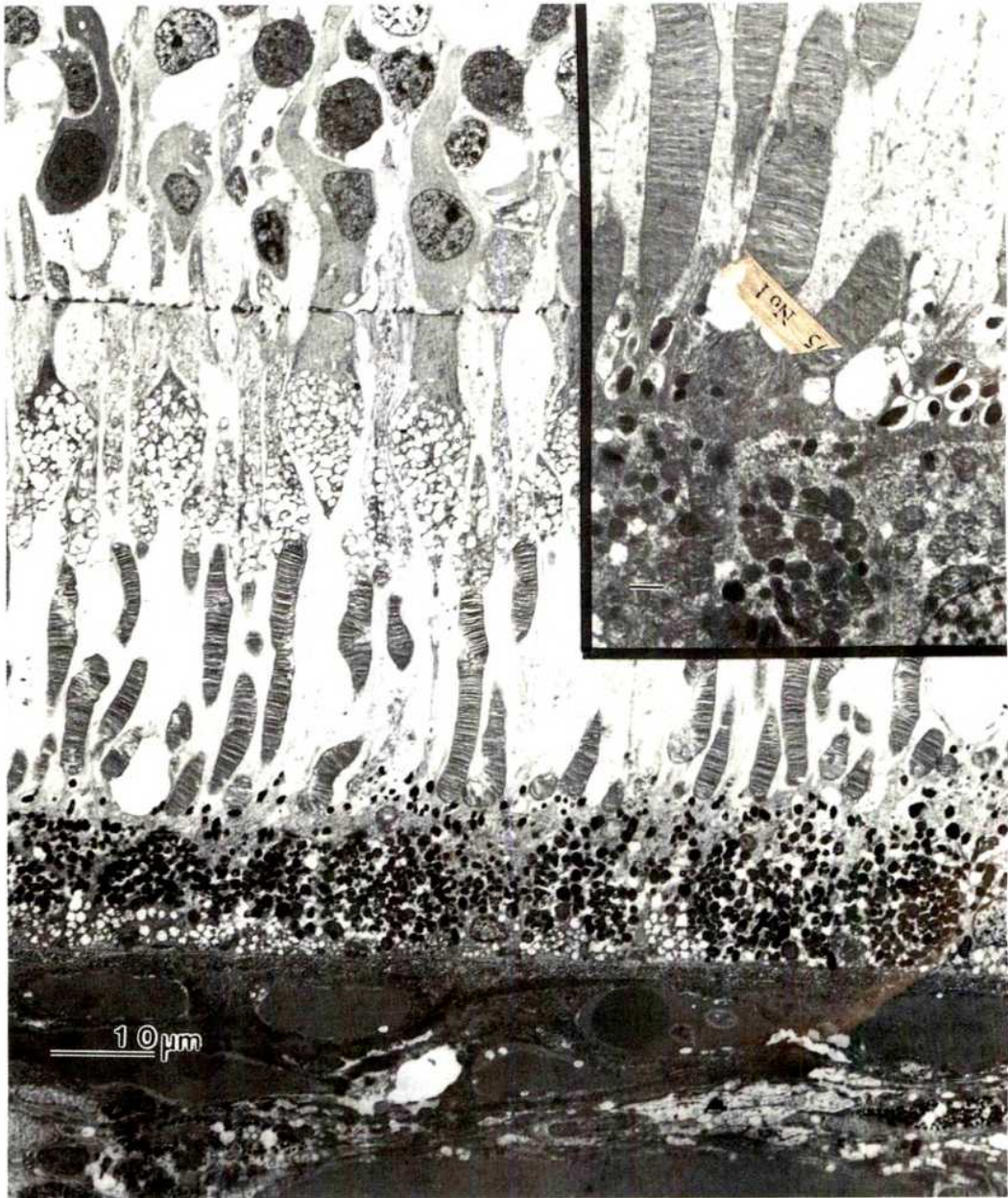
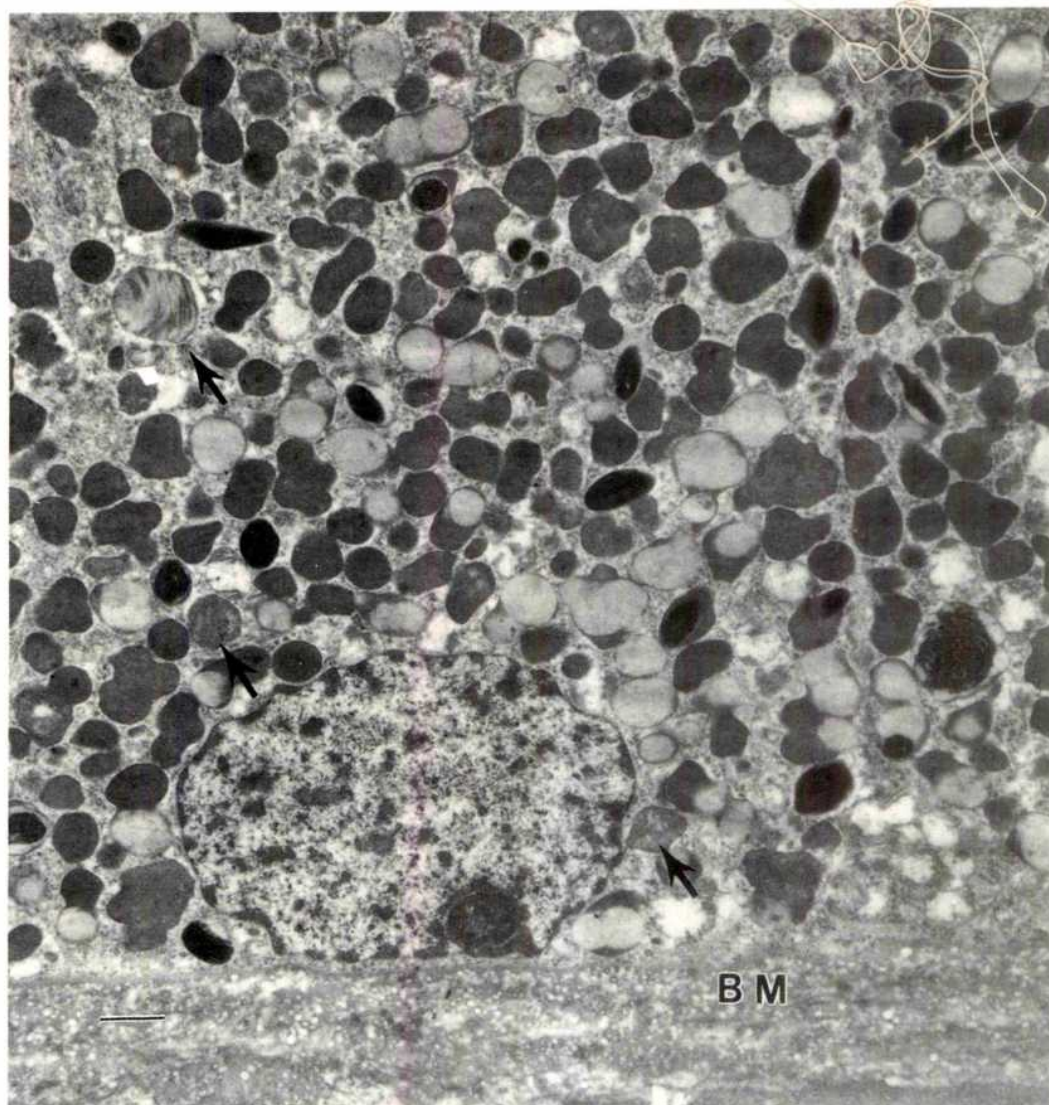


Figure 3 By electron microscopy the photoreceptors at the posterior pole are reduced in number but approach normal height. The RPE cells are enlarged by numerous intracytoplasmic inclusions. Inset shows RPE cell processes surrounding the tips of the photoreceptors. (Inset bar marker is 1 μm; osmicated tissue.)

Figure 4 The majority of the intracytoplasmic granules represent various stages of lipofuscin degradation and fusion with the formation of complexes with melanin granules. Photoreceptor phagosomes are indicated by arrows. Note that the cell nucleus is displaced to the basal area. BM: Bruch's membrane. This tissue was not osmicated. (Bar marker is 1 μ m.)



traumatised eye under investigation were at a very high level (600, SD 170) by comparison with the other specimens.

ELECTRON MICROSCOPY

The ultrastructural preservation of the pigment epithelium and the photoreceptor outer segments was acceptable, though there was evidence of mitochondrial dissolution. The findings will be discussed in three sections related to the topography of outer retina. Notable pathological changes were not observed in Bruch's membrane or the choriocapillaris in any region.

Regions where the outer segments approached normal size

Where by light microscopy the parafoveal photoreceptor layer appeared to be normal, it was apparent by electron microscopy that there some reduction in the numbers of photoreceptors, and the interphotoreceptor matrix was expanded (Fig 3). The outer segments showed focal disc fragmentation. The cytoplasm of the RPE cells contained large numbers of electron lucent round or oval lipofuscin granules (1 μ m diameter), melanin-lipofuscin complexes, and some photoreceptor disc phagosomes (Figs 4 and

5). It was noteworthy that photoreceptor disc material was also identifiable in phagosomes in the basal part of the cells. The phagolysosomes were of irregular outline and contained packed 10 nm to 15 nm light and dark bands within a relatively homogeneous electron dense matrix (Figs 4 and 5). Melanosomes were found throughout the cytoplasm, and melanosome dissolution was evidenced by the formation of structures which contained beaded strands (striated melanoprotein) and a well defined peripheral electron lucent rim (Fig 7).

Regions in which photoreceptors were present but stunted

The obvious abnormality (Figs 1b, 1c, and 6) was shortening and distortion of the outer segments of the surviving cells. The inner segments were depleted and shrunken, and there was a reduction in nuclei in the outer nuclear layer. The tips of the photoreceptor outer segments appeared as isolated ovoid masses within elongated frond-like processes from the RPE cells, but occasionally were found within the apical RPE cytoplasm (Fig 6). The RPE monolayer contained excessive quantities of lipofuscin bodies, which had a more granular appearance than those at the posterior pole. Phagolysosomes

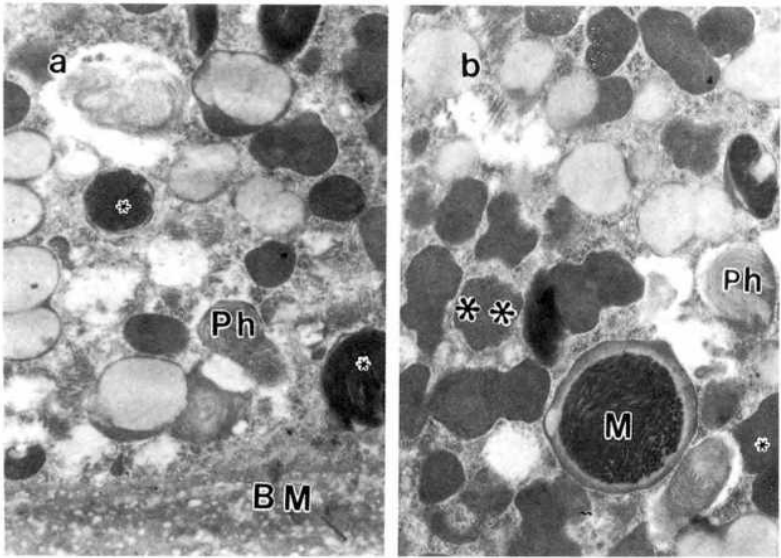


Figure 5 Details of the intracytoplasmic granules within the RPE. (a) Note the photoreceptor disc phagosomes (Ph) among the lipofuscin granules in the basal part of the RPE. BM: Bruch's membrane. In (b) occasional melanolysosomes (M) have a large round profile containing striated melanoprotein. In (a) and (b) premelanolysosomes (★) have a more electron-dense content than prephagolysosomes (★★). The relatively electronlucent structures are characteristic lipofuscin granules. This tissue was not osmicated. ($\times 12\,000$.)

and melanolysosomes were not found in the basal cytoplasm.

Regions of total photoreceptor cell atrophy

At the retinal periphery the photoreceptor cells were absent and replaced by glial cells (Fig 7). The processes from the glial cells interdigitated with those from the pigment epithelium, and in these regions some migrating RPE cells and some intraretinal macrophages were identified. The multilayered pigment epithelium in this region contained a few melanin granules and compound melanophagosomes, but lipofuscin granules were rare. The cells contained some electron dense granular material with a morphology consistent with that of breakdown products of blood. Macrophages containing similar electron dense particles and secondary melanophagolysosomes were found in the retina as solitary cells or in clumps.

Discussion

It is probably justifiable to explain the findings in

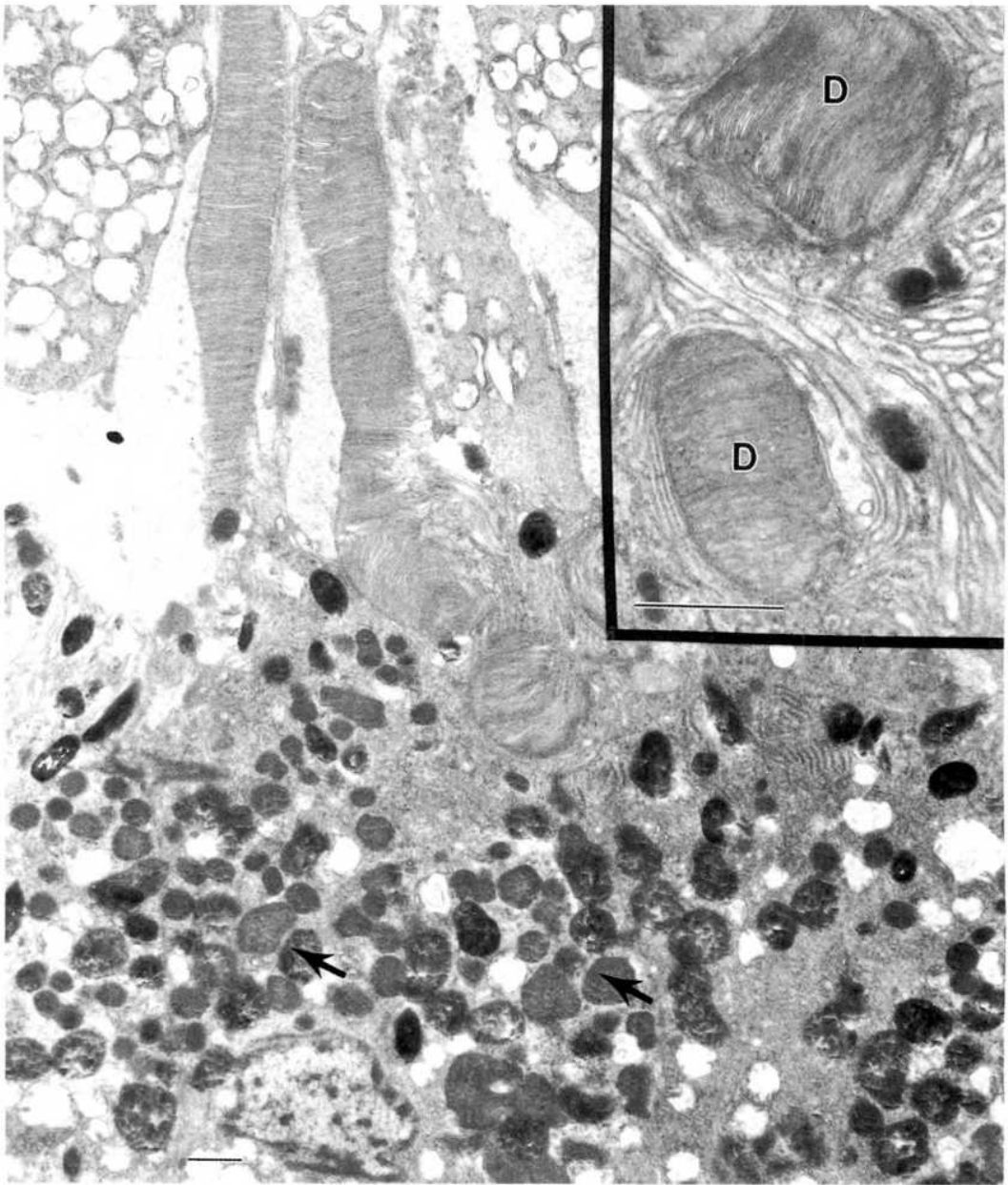
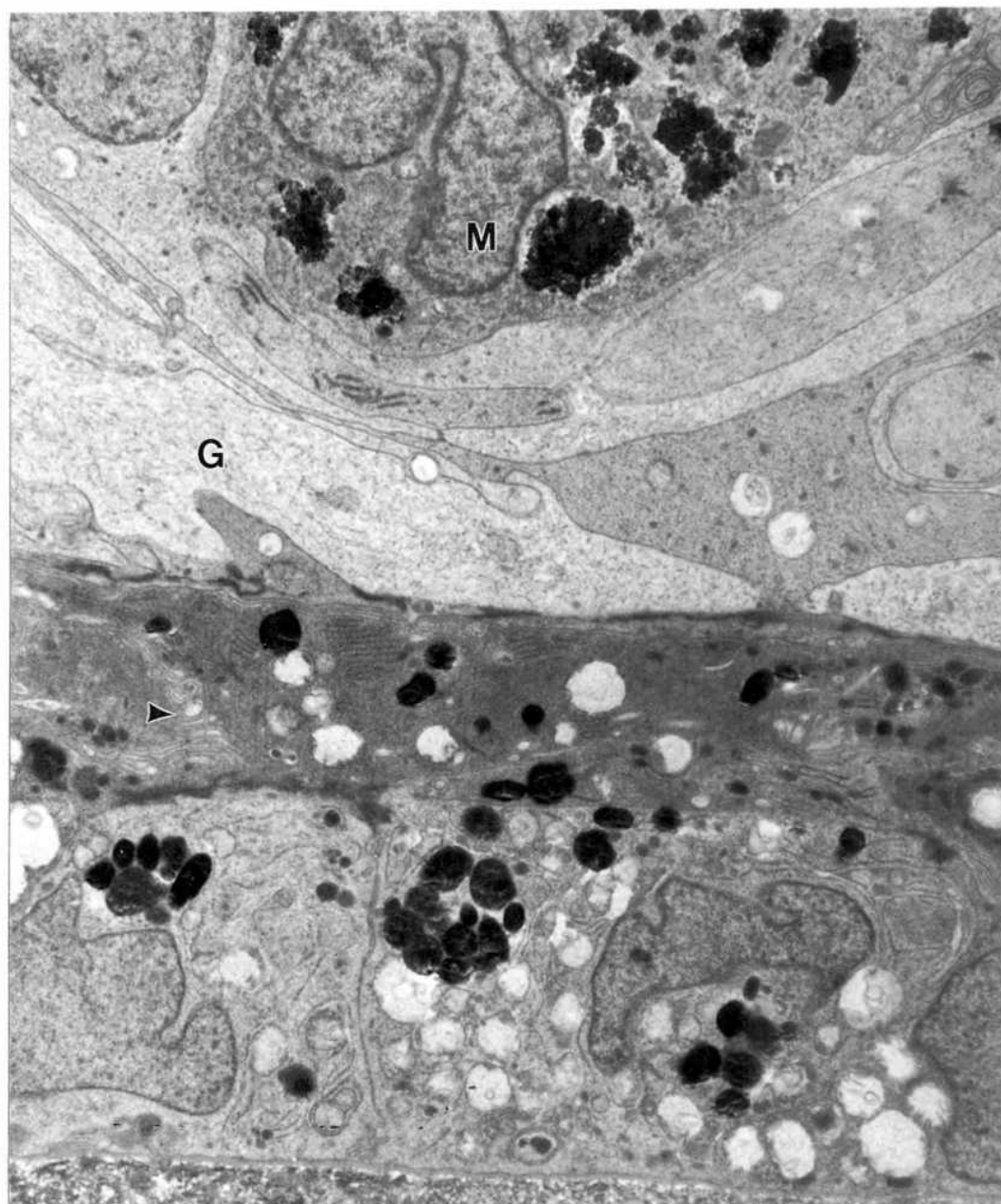


Figure 6 At the mid periphery the surviving photoreceptors are stunted, but the processes of the RPE surround the tips (D) of the outer segments (see inset). The RPE cells contain granular lipofuscin granules (arrows). (Osmicated tissue: bar is 1 μm .)

Figure 7 Toward the equator the photoreceptor cells are replaced by glial cells (G). Migrating RPE cells are linked by numerous interdigitations (arrowhead). A macrophage (M) containing melanophagosomes is present in the gliotic retina. Melanin granules and lipofuscin are sparse within the RPE. ($\times 5600$.)



the present case according to current opinion which holds that lipofuscin granules in the RPE represent the degradation products of shed photoreceptor discs,¹⁻⁷ though lipofuscin is also derived from the breakdown of endogenous cytoplasmic lipid-containing membranes such as mitochondrial products. In the normal RPE the number of lipofuscin granules per cell increases from the periphery to the posterior pole, and there is a measurable increase with age throughout the monolayer.^{4-6,12,13} Because there are no absolute standards for the microscopic measurement of lipofuscin, it is not possible to make direct comparison from our data to previously published work.^{4-6,13} However, our qualitative and quantitative estimates of lipofuscin autofluorescence in control tissue correspond in relative terms with information already available, and this strengthens the data obtained from the traumatised eye.

Our arbitrary value of 50 (SD 25) units for lipofuscin in the RPE of a 19-year-old was about 20% of that obtained from the 73-year-old eye, namely 250 (SD 50) units, which is not too far

from the 50% difference reported by Wing *et al*⁴ in a comparison between 30 years and 80 years. Feeney-Burns *et al*¹³ gave estimates of 88 granules per cell in the 1-20 age group and 208 granules per cell for the 61-100 age group, that is, about 40% lower in the younger age group. Accordingly we were encouraged that the mean values obtained from eyes (c) and (d) (Table 1) in which there was pathology which could have interfered significantly with the function of the RPE photoreceptor complex did not fall outside the upper and lower limits of the two controls.

The value of 600 (SD 170) (μm)²/50 μm for lipofuscin autofluorescence in a 55-year-old patient with post-traumatic RPE therefore reinforces the light microscopic and electron microscopic findings.

In our search of the literature relevant to RPE hyperlipofuscinosis we gained the impression that the condition was most commonly associated with photoreceptor atrophy and degeneration, which is in contrast to the good preservation of the photoreceptors observed in the case of traumatised eye under discussion.

Hyperlipofuscinosis in association with photoreceptor degeneration has been described by Weingeist *et al.*¹⁴ as a feature of Best's macular dystrophy, but those authors' electron micrographs do not demonstrate a concentration of lipofuscin as excessive as that described in the present case. As case of retinitis pigmentosa (complicated by angle closure glaucoma surgery and aphakia) has been reported by Kolb and Gouras,⁸ and in their case the retinal pigment epithelium appeared to contain large quantities of lipofuscin at the light microscopic level. More recently large quantities of lipofuscin were demonstrated in clusters of RPE cells in a choroideraemia carrier.⁹ The closest approach to the massive accumulation of RPE lipofuscin seen in the present case has been demonstrated in experiments on rats to study the effect of hypovitaminosis A and E.¹⁵⁻¹⁷ These experiments were designed to interfere with the mechanisms known to be involved in photoreceptor disc lipoprotein maintenance and in protection from peroxidation. Large quantities of lipofuscin accumulate in human ceroid lipofuscinosis¹⁰ and in animals similarly affected,^{11,18,19} but the ultrastructural characteristics of ceroid lipofuscin are dissimilar to the lipofuscin seen in normal aging and in the present case.

In contrast to hyperlipofuscinosis described above it was of interest that, when the RPE contained demonstrable iron, lipofuscin was not demonstrable. This was also a feature observed in the siderotic eye used for the present study (Table 1, case d). There was a similar dearth of lipofuscin in the RPE of the present case, in which iron and blood breakdown products were identified at the retinal periphery. The mechanisms by which soluble toxic iron salts interfere with RPE and photoreceptor metabolism are not known. However, at the posterior pole of the present specimen iron was not demonstrable histologically, and, since there was acceptable photoreceptor preservation, siderosis is an unlikely explanation for hyperlipofuscinosis.

It is worth reiterating that our patient has not suffered from familial or acquired systemic disease relevant to the changes in the enucleated eye in the period 1982-90 and his opposite eye has been normal. The pathological findings in the enucleated eye suggest that there was retinal detachment and widespread fragmentation of outer segments at the time of initial injury and that subsequently the retina reattached. The effect of the trauma may have been similar to that described in the pig model for blunt trauma.²⁰ In this model the acute dissolution and fragmentation of photoreceptors is followed by a gradual recovery, with restoration of inner and outer segments. In the present case there was an apparent recovery in the ability of the photoreceptor layer to produce outer segments at the posterior pole, with a failure at the mid periphery and the far periphery.

The RPE lipofuscin content appeared to mirror the status of the photoreceptors, but whether or not the accumulated lipofuscin was a manifestation of a single insult or a persisting low grade dysfunction in degradation remains open

to conjecture. The morphology of the accumulated materials within the RPE at the posterior pole was identical to that seen in the aging process^{3,6,12,13} and differed only in the greatly increased number of the particles. The identification of structures assumed to be photoreceptor phagosomes at various levels in the RPE cells points to some blockage of the degradative system at an early stage. We had anticipated some manifestations of disturbance in RPE exocytosis, which is a feature of normal aging⁷ and is recognised by the presence of curvilinear bodies in Bruch's membrane. It was of interest that Bruch's membrane and the choriocapillaris were totally unaffected by the excess of lipofuscin in the RPE monolayer, which contrasts with Best's macular dystrophy.¹⁴ Even though it is difficult to explain the pathogenesis, it seems justifiable to add this variant of hyperlipofuscinosis to the list of post-traumatic abnormalities which can occur in the human neural retina and RPE.

- 1 Young RW. Biological renewal. Applications to the eye. *Trans Ophthalmol Soc UK* 1982; 102: 42-75.
- 2 Bird AC, Marshall J. Retinal receptor disorders without known metabolic abnormalities. In: Garner A, Klintworth GK, eds. *Pathobiology of ocular disease*. New York: Dekker, 1982: 1167-220.
- 3 Feeney L. Lipofuscin and melanin of human retinal pigment epithelium. *Invest Ophthalmol Vis Sci* 1978; 17: 583-99.
- 4 Wing GL, Blanchard GC, Weiter JJ. The topography and age relationship of lipofuscin concentration in the retinal pigment epithelium. *Invest Ophthalmol Vis Sci* 1978; 17: 601-7.
- 5 Kitagawa K, Nishida S, Ogura Y. In vivo quantitation of autofluorescence in human retinal pigment epithelium. *Ophthalmologica* 1989; 199: 116-21.
- 6 Weiter JJ, Delori FC, Wing GL, Fitch KA. Retinal pigment epithelial lipofuscin and melanin and choroidal melanin in human eyes. *Invest Ophthalmol Vis Sci* 1986; 27: 145-52.
- 7 Pauleikhoff D, Harper A, Marshall J, Bird AC. Aging changes in Bruch's membrane. *Ophthalmology* 1990; 97: 171-8.
- 8 Kolb H, Gouras P. Electron microscopic observations of human retinitis pigmentosa, dominantly inherited. *Invest Ophthalmol Vis Sci* 1974; 13: 487-98.
- 9 Flannery JG, Bird AC, Farber DB, Weleber RG, Bok D. A histopathological study of a choroideraemia carrier. *Invest Ophthalmol Vis Sci* 1990; 31: 229-36.
- 10 Hittner HM, Zeller RS. Ceroid-lipofuscinosis (Batten's disease). Fluorescein angiography electrophysiology, histopathology, ultrastructure, and a review of amaurotic familial idiocy. *Arch Ophthalmol* 1975; 93: 178-83.
- 11 Graydon RJ, Jolly RD. Ceroid-lipofuscinosis (Batten's disease): sequential electrophysiologic and pathologic changes in the retina of the ovine model. *Invest Ophthalmol Vis Sci* 1984; 25: 294-301.
- 12 Feeney-Burns L, Gao CL, Berman ER. The fate of immunoreactive opsin following phagocytosis by pigment epithelium in human and monkey retinas. *Invest Ophthalmol Vis Sci* 1988; 29: 708-19.
- 13 Feeney-Burns L, Hilderbrand ES, Eldridge S. Aging human RPE: morphometric analysis of macular, equatorial and peripheral cells. *Invest Ophthalmol Vis Sci* 1984; 25: 195-200.
- 14 Weingeist TA, Kobrin JL, Watzke RC. Histopathology of Best's macular dystrophy. *Arch Ophthalmol* 1982; 100: 1108-14.
- 15 Robinson WG, Kuwabara T, Bieri JG. The roles of vitamin E and unsaturated fatty acids in the visual process. *Retina* 1982; 2: 263-81.
- 16 Robinson WG, Kuwabara T, Bieri JG. Deficiencies of vitamins E and A in the rat. Retinal damage and lipofuscin accumulation. *Invest Ophthalmol Vis Sci* 1980; 19: 1030-7.
- 17 Robinson WG, Kuwabara T, Bieri JG. Vitamin E deficiency and the retina. Photoreceptor and pigment epithelial changes. *Invest Ophthalmol Vis Sci* 1979; 7: 683-90.
- 18 Armstrong DA, Siakotos A, Koppang N, Connole E. Studies on the retina and the pigment epithelium in hereditary canine ceroid lipofuscinosis. The distribution of enzymes in the whole retina and pigment epithelium. *Invest Ophthalmol Vis Sci* 1978; 17: 608-17.
- 19 Siakotos AN, Armstrong D, Koppang N, Connole E. Studies on the retina and the pigment epithelium in hereditary canine ceroid lipofuscinosis. II. The subcellular distribution of lysosomal hydrolases and other enzymes. *Invest Ophthalmol Vis Sci* 1978; 17: 618-33.
- 20 Blight R, Hart JCD. Structural changes in the outer retinal layers following blunt mechanical non-perforating trauma to the globe. An experimental study. *Br J Ophthalmol* 1977; 61: 573-87.

Decalcification of a choroidal osteoma

Susan N Trimble, Howard Schatz

Abstract

A 56-year-old man presented with a clearly defined orange tumour in the posterior pole of his left eye. A choroidal osteoma was suspected, and ultrasonography confirmed the diagnosis. Fluorescein angiography demonstrated subretinal neovascularisation on the nasal edge of the tumour, which was treated with krypton laser photocoagulation twice. Recurrent subretinal neovascularisation occurred one year later and was not amenable to treatment. Three years after the patient first presented, thinning of the tumour was noted on follow-up examination. During the next 15 months the tumour completely disappeared, leaving an area of retinal pigment epithelial and choroidal atrophy. Total decalcification of the choroidal osteoma was demonstrated by ultrasonography.

Choroidal osteomas are juxtapapillary choroidal lesions which contain bone, and have been recognised since 1978.^{1,2} We report a second case of choroidal osteoma which gradually disappeared after laser treatment for subretinal neovascularisation.³ In both cases decalcification occurred, leaving an area of atrophic retinal pigment epithelium and choriocapillaris.

Case report

In June 1982, a 56-year-old white male was seen in consultation with a three- or four-week history of distorted vision in his left eye. The history was negative except for past thyroid cancer in 1955. A thyroid resection was done initially, and metastatic rib cage tumours were removed in 1963. When he presented to us, his visual acuity was 20/20 in the right eye and 20/50 in the left eye. A well defined, slightly elevated mass was seen in the posterior pole of the left eye. The mass was orange centrally and was yellow-white where the retinal pigment epithelium was thinned along

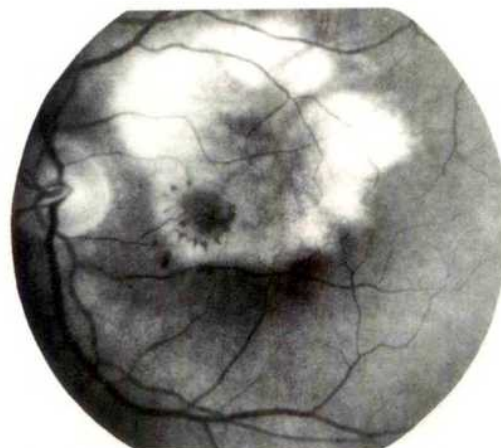


Figure 1B Red-free photograph left macula. Note the choroidal osteoma in the upper part of the macula. There is a patch of subretinal neovascularisation in the papillomacular bundle adjacent to the fovea. Note a few spots of subretinal haemorrhage.

the margin (Fig 1A). Fluorescein angiography demonstrated the tumour and subretinal neovascularisation located nasal to the left fovea (Figs 1 B-D). On the ultrasonogram there was very high reflectivity and extreme acoustic shadowing of orbital fat behind the globe consistent with the diagnosis of choroidal osteoma.

The subretinal neovascularisation was treated with krypton laser photocoagulation. Two months later the patient's vision dropped from 20/40 to 8/200, and recurrent subretinal neovascularisation was again treated with laser. His vision did not improve, though the macula remained dry for the next year. In August 1983 there was a new haemorrhage with serous detachment in the macula, and recurrent subretinal neovascularisation was defined on the fluorescein angiogram (Figs 2, A-C). Since then his vision has remained 3/200.

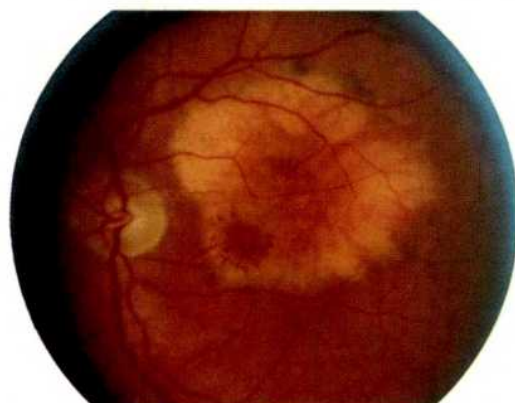


Figure 1A June 1982. Well defined choroidal osteoma with reddish centre and yellow-white edge. Note subretinal neovascularisation at inferior nasal edge of tumour.

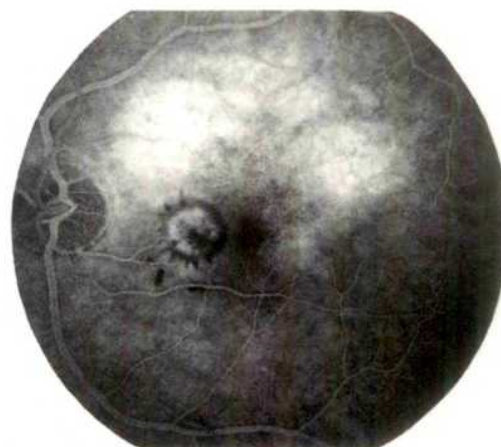


Figure 1C Midphase angiogram showing moderate fluorescence from the choroidal osteoma as well as hyperfluorescence from the ring of subretinal neovascularisation nasal to the fovea. The haemorrhage hypofluoresces.

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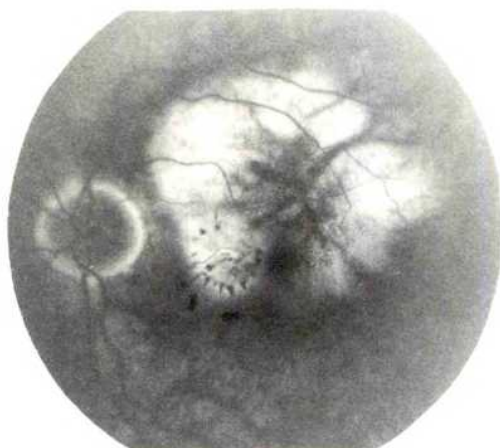


Figure 1D Late phase fluorescein angiogram shows that the choroidal osteoma stains and there is leakage into the subretinal space from the patch of subretinal neovascularisation.



Figure 2C Late phase angiogram shows leakage from the patch of subretinal neovascularisation below and staining of the choroidal osteoma and previous laser treatment.

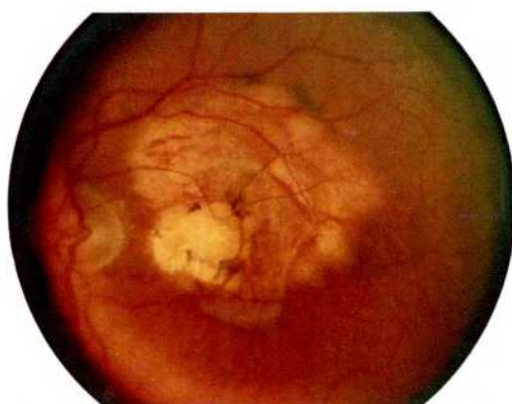


Figure 2A Fourteen months later. The patch of subretinal neovascularisation has been treated, and there is an atrophic scar in the papillomacular bundle. The subretinal neovascularisation has recurred just below the fovea. The choroidal osteoma appears thinner with visualisation of choroidal vessels.

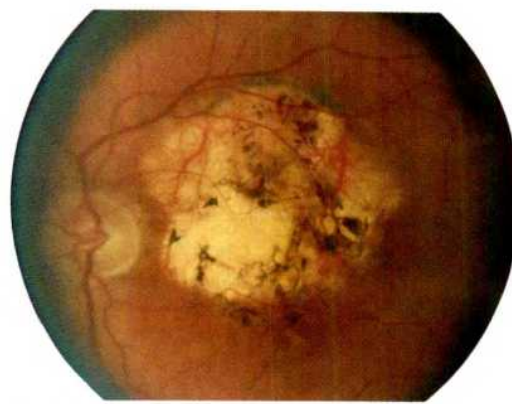


Figure 3 July 1986 Complete decalcification of the choroidal osteoma has occurred leaving an area of pigment epithelial and choroidal atrophy. Clumps of pigment are seen.

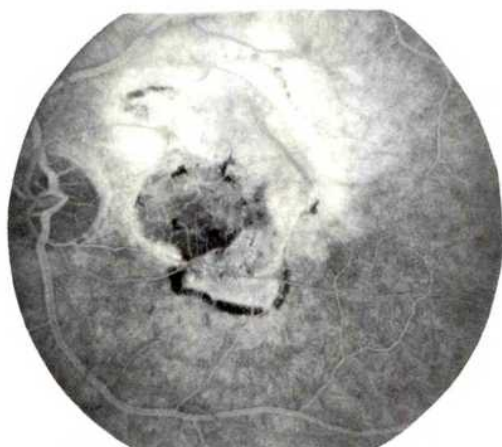


Figure 2B Midphase angiograms showing hyperfluorescence from the patch of subretinal neovascularisation below the macula with a surrounding ring of subretinal haemorrhage (hypofluorescent ring), atrophy from the previous laser nasal to the fovea, and thinning of the choroidal osteoma above.

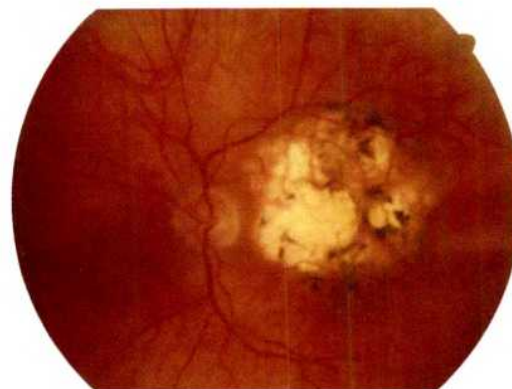


Figure 4A September 1988. Additional chorioretinal atrophy has occurred since July 1986.

chorioretinal atrophy at the tumour site (Figs 4A-D).

Discussion

Choroidal osteomas are yellow-white or orange, peripapillary lesions with discrete, well defined borders. They are seen most often in young white, healthy females. The aetiology is not known, but one factor may be intraocular inflammation. They have been found in eyes with associated inflammatory diseases.^{4,6} We have reported a case of an osteoma that developed

In April 1985 the tumour appeared to be thinning, and retinal pigment epithelial atrophy was noted. Ultrasonography still showed calcification. Fifteen months later the pigment epithelium was more atrophic (Fig 3), and total decalcification was confirmed by ultrasonography. Examination in 1988 revealed additional

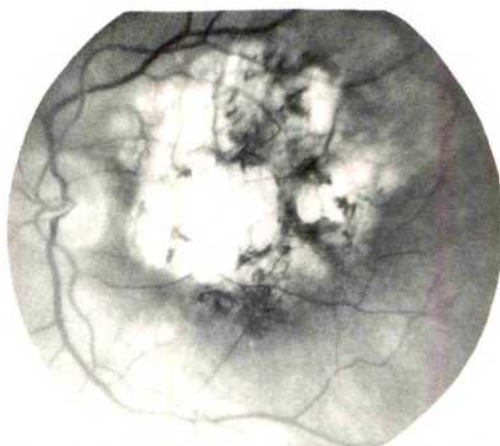


Figure 4B Red-free photograph. Atrophic areas are seen at the previous tumour site. There is thinning and loss of retinal pigment epithelium and choroid with scattered pigment clumping.

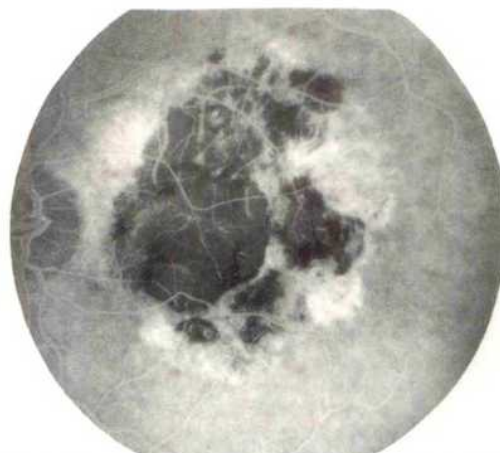


Figure 4C Mid-phase angiography shows hypofluorescence in the areas of chorioretinal atrophy. In the surrounding retina is hyperfluorescence due to visualisation of choriocapillaris where overlying retinal pigment epithelium is defective.

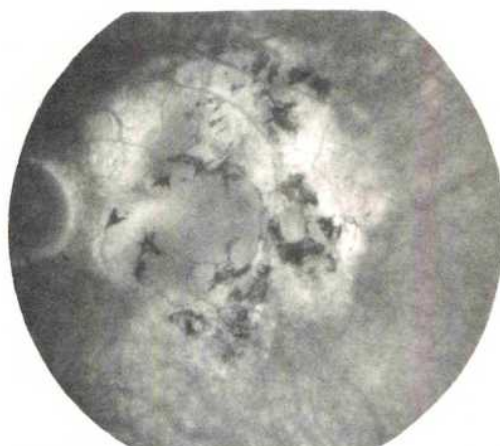


Figure 4D Late stage angiogram shows hyperfluorescence from scleral staining. Pigment clumps are hypofluorescent.

at a site where focal choroiditis had occurred five years previously.⁷

Unexpected decalcification and disappearance of a choroidal osteoma was observed and first reported by us in 1988.³ In that case a 23-year-old woman had a choroidal osteoma confirmed by ultrasonography and orbital tomography. Over five years it grew slowly. Subretinal neovascularisation developed and was treated with argon laser photocoagulation. Gradual thinning and tumour decalcification followed. Eighteen months later complete decalcification and atrophy had occurred. At that time a bed of pigment epithelial and choriocapillaris atrophy remained. Disappearance of the choroidal osteoma and loss of calcium was confirmed by fluorescein angiography and ultrasonography.

A second case is reported here in a 56-year-old man. The development of parafoveal subretinal neovascularisation occurred in both patients and

was treated with laser photocoagulation. Whether this factor is of any significance in the subsequent disappearance of the tumour is unknown.

Resorption of bone is initiated when there is osteoclast formation adjacent to bone. Osteoclasts are multinucleated cells formed by the fusion of mononuclear precursors. In addition mononuclear phagocytic inflammatory cells (monocytes and macrophages) may participate in resorption of normal or pathological bone.

Reporting this second case is important because the phenomenon of decalcification and disappearance of choroidal osteomas could be part of the natural course of the disease. Since choroidal osteomas were first identified in 1978, most cases have been followed up for a decade or less. Another factor in both our cases is that each had laser treatment for subretinal neovascularisation. Perhaps a cascade of osteoclast activity was initiated after it which led to the disappearance of the osteoma. In a patient who presents with a well defined area of chorioretinal atrophy in the posterior pole a decalcified choroidal osteoma should be considered in the differential diagnosis.

- 1 Williams AT, Font RL, VanDyk HJL, Riekhof FT. Osseous choristoma of the choroid simulating a choroidal melanoma. *Arch Ophthalmol* 1978; **96**: 1874-7.
- 2 Gass JDM, Guerry RK, Jack RL, Haris G. Choroidal osteoma. *Arch Ophthalmol* 1978; **96**: 428-35.
- 3 Trimble SN, Schatz H, Schneider GB. Spontaneous decalcification of a choroidal osteoma. *Ophthalmology* 1988; **95**: 631-4.
- 4 Kline LB, Skalka HW, Davidson JD, Wilmes FJ. Bilateral choroidal osteomas associated with fatal systemic illness. *Am J Ophthalmol* 1982; **93**: 192-97.
- 5 Gass JDM. *Stereoscopic atlas of macular diseases*. 3rd ed. St. Louis: 1987: 1: 152, 153, 180.
- 6 Katz RS, Gass JDM. Multiple choroidal osteomas developing in association with recurrent orbital inflammatory pseudotumour. *Arch Ophthalmol* 1983; **101**: 1724-7.
- 7 Trimble SN, Schatz H. Choroidal osteoma after intraocular inflammation. *Am J Ophthalmol* 1982; **96**: 759-64.

LETTERS TO THE EDITOR

Withdrawal of 0.6% GlauLine (metipranolol)

SIR,—Following reports of a number of cases of anterior uveitis associated with the 0.6% strength of our ophthalmic β blocker, GlauLine, we are now withdrawing this strength from the market. The 0.1% and 0.3% concentrations remain available for prescription as usual.

Our advice to ophthalmologists and general practitioners is that all patients managed with 0.6% GlauLine should have their medication reviewed as soon as possible and changed to the 0.3% strength or to an alternative ocular hypotensive. If a patient presents a prescription for GlauLine 0.6% following this notification, pharmacists are asked to contact the prescriber to confirm that it should be dispensed.

As we appreciate the difficulty in seeing all patients to make this change immediately, we will continue to make GlauLine 0.6% available until 1 October 1990 to ensure that their prescriptions can be met in the interim. We will be recalling unused stock at a later stage.

We have written individually to ophthalmologists, general practitioners, and pharmacists concerning the withdrawal and would be grateful if you could include reference to it in your publication.

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Anaphylactic reaction following application of chloramphenicol eye ointment

SIR,—Ophthalmic preparations of chloramphenicol are favoured by ophthalmologists because of their broad spectrum of antibacterial activity, low corneal toxicity, the availability of preservative free solutions, and their ability to provide therapeutic levels in aqueous humour after topical application.¹ Chloramphenicol eye ointment is therefore commonly used in external eye infections. To the best of our knowledge this is the first report of an anaphylactic reaction following administration of chloramphenicol eye ointment.

A 30-year-old healthy man with no history of allergy underwent in 1987 excision of a chalazion cyst in his right lower lid under local anaesthesia with lignocaine 1%. The excision was uneventful, and the eye was patched with chloramphenicol eye ointment 5%. Three hours after the procedure, angioedema and urticaria developed. The patient was referred to the nearest emergency room and was admitted to hospital because of severe angioedema, urticaria, and bronchospasm, which necessitated treatment with adrenaline and intravenous corticosteroids for two days. As the only medications used were the local anaesthetic

and the ointment, it was presumed that the reaction was to the local anaesthetic. In 1989, however, the patient experienced the same episode again, this time after applying topical chloramphenicol on a finger wound of his daughter's. Once again his condition necessitated admission to hospital and vigorous treatment with adrenaline and corticosteroids. The diagnosis of allergy to chloramphenicol was made, and the patient was cautioned accordingly.

Systemic effects of eye ointments result from absorption through conjunctival membranes, or from drainage down the lacrimal duct and absorption through nasopharyngeal mucosal membranes. The allergic reaction is caused by systemic circulation of the antigen. The occurrence of an anaphylactic reaction following systemic administration of chloramphenicol is rare.² Six reports involving 10 patients with presumptive anaphylaxis due to chloramphenicol were reviewed by Palchick *et al.*³ The occurrence of anaphylactic reaction after administration of topical chloramphenicol to the skin has been reported in two patients.⁴ The only systemic side effect after application of chloramphenicol to the eye is aplastic anaemia, which has been reported in five cases as reviewed by Brodsky *et al.*⁵ We did not find any description of anaphylactic reaction following administration of chloramphenicol eye ointment.

It appears to be justifiable in our patient to attribute the two allergic reactions to chloramphenicol eye ointment. It seems to us, that though anaphylaxis is surely rare following the use of chloramphenicol eye ointment, physicians should be aware of this complication to aid early detection and treatment.

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- 1 Beasley H, Boltralik JJ, Baldwin HA. Chloramphenicol in aqueous humor after topical application. *Arch Ophthalmol* 1975; 93: 184.
- 2 Reynolds JEF, ed. *Martindale: The Extra Pharmacopoeia*. London: Pharmaceutical Press, 1989: 106, 186, 192.
- 3 Palchick BA, Funk EA, McEntire JE, Hamory BH. Anaphylaxis due to chloramphenicol. *Am J Med Sci* 1984; 288: 43-5.
- 4 Schewach-Miller M, Shpiro D. Urticaria and angioedema due to topically applied chloramphenicol ointment. *Arch Dermatol* 1985; 121: 587.
- 5 Brodsky E, Zeidan Z, Biger Y, Schneider M. Topical application of chloramphenicol eye ointment followed by fatal bone marrow aplasia. *Isr J Med Sci* 1989; 25: 54.

Eye surgery in Eritrea

SIR,—We have just finished a ward round of 27 patients: 24 extracapsular cataract extractions with posterior chamber intraocular lenses, one anterior chamber intraocular lens, and two trabeculectomies. All the eyes look good; corneae were clear and only the anterior chamber lens a little hot.

All were done by an Eritrean in the air

conditioned theatre of this rocket blasted hospital. We brought the equipment and lenses from Australia, and instructed and supervised. They did them.

This eye surgery is the first to be done here since the Eritreans recaptured Massawa Port some five months ago. It is certainly the first series of modern cataract operations to be done in this part of the world.

Many of the patients come from Danakel, said to be the hottest place on earth. One such man, an Afar of no more than 40 years, had the whitest of white cataracts. Like most of the others he was blind. But not now. In this place, 'somewhere east of Suez, where... a man can raise a thirst,' it is hard not to see a link between light, heat, and cataract. After all, Dahlak blindness (Labrador keratopathy, climatic droplet keratopathy) is common here, as are corneae burgeoning with clusters of spheroidal droplets.

We came via Sudan and the arid hills of Northern Eritrea. There, in a base hospital camouflaged and half underground, we did or instructed Eritreans (all but one 'medically qualified'), while they did another 25 or so cataracts with intraocular lenses. Locally produced Ringer's lactate was used, with all corneae lustrous.

Travelling is tough by any standard—done at night in four-wheel drive vehicles over river beds. The equipment, previously tested in rural Nepal and outback Australia, is well packed and so travels without damage.

Africa, with about 500 million people, needs at least 3½ million eye operations each year just to keep up with cataract, glaucoma, and trachoma blindness. However, it has only about as many eye surgeons as Australia with its population of 17 million. The Eritrean medical assistants have good hands and need only microscope training and surgical tuition to become modern eye surgeons. As surgeons emerged from barbers, so must medical assistants in Africa become the ones to shoulder the enormous eye surgery load of this continent.

Eritrea's battle to regain its identity has lasted almost 30 years. We have seen some of that conflict's casualties. In a single camp 150 young people are blind from multiple perforating injuries and intraocular foreign bodies. Most of the injuries would defy the skills of even the best vitrectomist, corneal grafter, and anterior segment reconstructor combined. We have also seen many cases of blinding sympathetic ophthalmitis. Perhaps earlier and more skilful microscopic trauma repair would prevent some of this.

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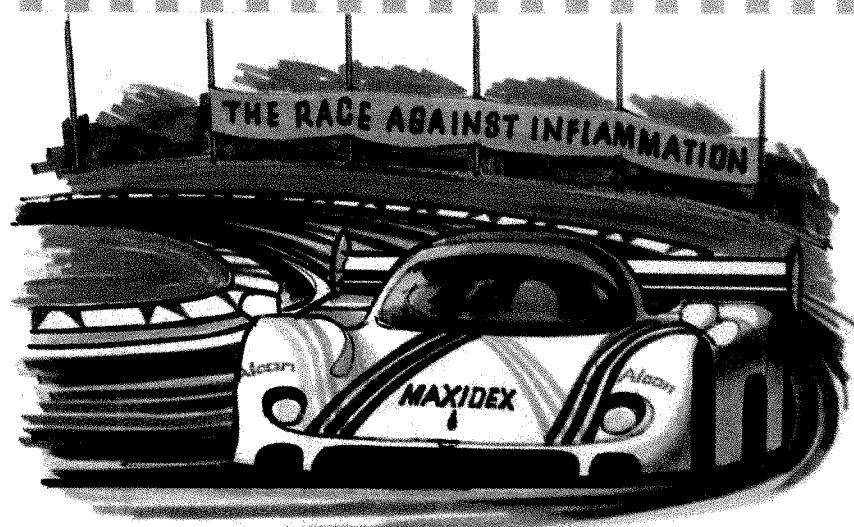
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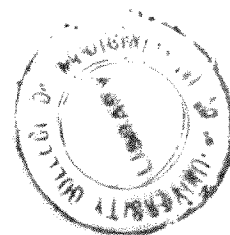
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BRITISH JOURNAL OF OPHTHALMOLOGY



Editorial

The ocular pulse

The early ophthalmoscopists overcame the deficiencies of their instrument by employing highly tuned powers of observation inspired by the knowledge that they trod where no man had trod before. To us more pedestrian 20th century ophthalmic observers they seem to have recorded signs which are difficult to identify even with our modern halogen powered equipment. Among the smaller signs detected was the spontaneous pulsation of the retinal arteries. Duke-Elder, in summarising the work of these early pioneers, noted that both Donders (1852) and Becker (1872) drew our attention to these pulsations.¹

The amplitude of this arterial pulse is dampened by the lack of distensibility of the ocular coats. Unless there was an area of weakness in the coats of the eye, such as a posterior staphyloma or a nearly perforated corneal ulcer,¹ the arterial pulse was transformed into a volume pulse of such low amplitude that it was invisible to even the 19th century ophthalmologists.

The widespread adoption of applanation tonometry, by allowing the routine observation of pulsating mires at the slit-lamp, highlighted the existence of such a volume pulse and its variations in physiological and pathological states. It is well recognised that a reduction in movement of the mires may occur in myopia, ocular disease, or carotid insufficiency.

Quantification of this ocular pulse became possible when Perkins modified an applanation prism by replacing the contact surface with a distensible film. This film allowed continuous transmission of the ocular pulse to a pressure transducer, which in turn generated a pulse trace.² He was able to define the normal pulse amplitude as >1.5 mmHg and showed that an interocular difference in pulse amplitude rarely exceeded 0.5 mmHg. Using these data he identified carotid insufficiency from dissimilar or reduced pulse amplitudes.² He also noted that his device could provide a reasonably accurate IOP measurement as well.

Langham adapted the pneumotonometer for a similar purpose, using it to provide a wave form of the ocular pulse. By analysing this wave form, its amplitude, and the heart rate he was able to derive values for the pulsatile component of blood flow.³ It needs to be remembered that non-pulsatile blood flow, as revealed by Doppler ultrasound studies of the ophthalmic artery,⁴ has not been estimated by this technique.

The versatility of the pneumotonometer, allowing measurements of the IOP to be made while the subject varied his posture, has allowed Trew and Smith to re-evaluate the relationship of changes in IOP to changes in posture, as well as assess pulsatile ocular blood flow. In two papers in this issue the authors confirm that, while the assumption of a

supine posture is followed by an increase in IOP in both normal persons and glaucoma patients, the rise was far greater in the latter group. They also report that this IOP change was associated with a fall in pulsatile ocular blood flow, which was not improved despite a fall in IOP with topical timolol therapy.

As the increase in IOP seen on adopting the supine position is greatest in glaucoma patients, it could be suggested that a compromised ocular circulation would be put at further risk by any additional increase in IOP, as well as by a possible fall in the systemic blood pressure in the sleeping, treated hypertensive patient. Indeed that idea has been put forward as a major cause of progressive visual loss in low tension glaucoma. The authors suggest that these pressure changes are associated with a reduction in pulsatile ocular flow in patients with primary open-angle glaucoma on adopting the supine position and that this reduction is not reversed despite lowering of IOP with topical β blockers.

What is the significance of these findings for the practising ophthalmologist? Firstly, glaucoma patients have an exaggeration in the posture induced IOP increase, which may be associated with postural hypotension in the treated hypertensive patient, and this might reduce ocular flow during sleep. However, it has yet to be demonstrated that glaucoma patients are more liable to have suffered episodes of visual loss during sleep (in contrast to the timing of episodes of ischaemic optic neuropathy). There is therefore no proved need to suppress this IOP increase, though, perhaps by a nightly acetazolamide tablet it may help the occasional patient.

Secondly, what is the relevance of pulsatile ocular flow to the circulation at the optic nerve in glaucomatous eyes? It must be remembered that $>90\%$ of ocular blood flow is taken by the choroidal circulation and that the optic nerve circulation accounts for a minute fraction. Any recorded changes can reflect changes only in the former. This casts doubt on attempts to relate total flow changes to optic nerve disease. Unless it can be shown that changes in the former mirror or induce changes in the latter, interpretation of treatment-induced modifications in flow must be treated with caution.

R HITCHINGS

1 Duke-Elder S. The development form and function of the visual apparatus. *Textbook of ophthalmology*. St Louis, Mosby, 1944; 1: 398-9.

2 Perkins ES. The ocular pulse and intraocular pressure as a screening test for carotid artery stenosis. *Br J Ophthalmol* 1985; 69: 676-80.

3 Langham ME, Farrell MA, O'Brien V, Silver DM, Schilder P. Blood flow in the human eye. *Acta Ophthalmol (Kgh)* 1989; 67 (suppl 191): 9-12.

4 Canning C, Restori M. Doppler ultrasound studies of the ophthalmic artery. *Eye* 1988; 2: 92-5.

ORIGINAL ARTICLES

Postural studies in pulsatile ocular blood flow: I. Ocular hypertension and normotension

D R Trew, S E Smith

Abstract

Measurements of pulsatile ocular blood flow (POBF) have been recorded in a group of healthy, ocular normotensive volunteers and ocular hypertensive patients recruited from outpatients. Use of a pneumotonometric probe linked to a Langham ocular blood flow system enabled readings of intraocular pressure and its variation with heart rate (ocular pulse) to be taken in erect and supine positions. Pulsatile ocular blood flow was calculated from these values by means of the pressure-volume relationship previously described for living human eyes. Assumption of the supine posture was accompanied by a significant rise in intraocular pressure; in normal eyes (mean, with SEM) (3.1 (0.4) mmHg, $p < 0.0001$) and to a greater extent in ocular hypertensive eyes (4.7 (0.6) mmHg, $p < 0.0001$). The POBF did not differ significantly between normotensive and ocular hypertensive groups in either the erect or supine postures. In both groups, however, assumption of the supine posture was accompanied by a significant fall in POBF (normals: -121 (21) $\mu\text{l}/\text{min}$, $p < 0.0001$; ocular hypertensives: -75 (16) $\mu\text{l}/\text{min}$, $p < 0.0002$). These reductions in POBF represent decrements of 27.5 (3.0)% and 17.1 (3.8)% respectively. Pulsatile ocular blood flow is reduced in the supine posture, and this may result in tissue hypoxia in subjects at risk of developing glaucoma. A companion paper describes the measurement of POBF in a group of patients with chronic open angle glaucoma treated with topical timolol 0.25%.

A rise in intraocular pressure (IOP) on lying down is a well described phenomenon and has been confirmed by means of several different techniques. It occurs in both healthy subjects¹⁻⁴ and to a greater extent in ocular hypertensives.⁵ The apparent ability of many eyes to withstand raised pressures without developing glaucomatous changes has caused much speculation. Comment has often centred on the protective role of the ocular blood supply, particularly to the optic nerve head, in the hypertensive group.⁶⁻⁸

An adequate blood flow to this region is essential in maintaining normal visual function, but both experimentally and clinically rates of flow have always been difficult to measure owing to the inaccessibility of the posterior

ciliary arteries. In recent years a number of experimental techniques have been used to measure regional flow rates, particularly radio-labelled microspheres⁹ and more recently, and indirectly, by 2-deoxyglucose uptake¹⁰ and iodoantipyrine clearance.⁶ There are obvious limitations to these methods in that investigation is confined to animals which must be killed for the eyes to be assessed in the laboratory and results obtained. There has also been renewed interest in the use of indocyanine green dye angiograms attempting to characterise pulsatile choroidal blood flow.¹¹

Established techniques in human subjects have concentrated on a number of clinical applications. Laser Doppler velocimetry has been used to measure retinal flow,^{12,13} and attempts have also been made to assess optic nerve head blood velocity,¹⁴ but the depth of measurement is difficult to clarify and may represent only superficial retinal flow. Photographic and fluorescein angiographic methods have also been used to measure mean retinal circulation time,¹⁵⁻¹⁷ and videoangiography promises useful information for the future.¹⁸

However, the retinal circulation contributes only 5% approximately of the total ocular circulation^{19,20} and does not supply the optic nerve head, which is served essentially by the posterior ciliary circulation.²¹ The ability to measure total ocular flow incorporating the ciliary supply, which must be its major component, may therefore give a better understanding of the haemodynamics of this critical region.

Use of a pneumotonometric probe linked to a Langham ocular blood flow system permits the calculation of the pulsatile component of ocular blood flow. The values are derived from an analysis of the IOP pulse waveform, the heart rate, and the amplitude between systolic and diastolic intraocular pressures (the ocular pulse), factors which are discussed later in the paper.

This study has been undertaken to record derived values of POBF in healthy ocular normotensive and hypertensive subjects and to measure any changes related to posture.

Subjects and methods

SUBJECTS

Eighteen healthy ocular hypertensive (OH) patients were recruited from outpatients. Ocular

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Table 1 Postural changes in ocular and systemic variables concerned in pulsatile ocular blood flow in healthy ocular normotensive and hypertensive subjects: mean (SEM)

Variable	Normotensives				Hypertensives			
	Erect	Supine	Difference	p	Erect	Supine	Difference	p
Heart rate (bpm)	70 (1.5)	59 (1.5)	-11 (1.6)	<0.0001	81 (3.5)	65 (3.0)	-16 (1.9)	<0.0001
Mean BP (mmHg)	97.4 (2.6)	90.8 (2.9)	-6.6 (2.0)	<0.004	104.9 (2.7)	98.1 (2.1)	-6.8 (2.0)	<0.005
IOP (mmHg)	16.2 (0.7)	19.3 (0.7)	+3.1 (0.4)	<0.0001	22.6 (0.7)	27.3 (0.7)	+4.7 (0.6)	<0.0001
Pulse amplitude (mmHg)	1.8 (0.2)	1.8 (0.2)	0	NS	2.1 (0.1)	2.4 (0.2)	+0.3 (0.1)	<0.05
POBF (μ l/min)	453 (46)	332 (40)	-121 (21)	<0.0001	427 (26)	352 (26)	-75 (16)	<0.0002

NS=not significant.

hypertension was defined as a Goldmann intra-ocular pressure of 22 mmHg or more when seated, on at least three occasions in the clinic. There were 10 males and eight females with a mean age of 63.1 years (range 26–78). Twenty healthy volunteers (five males, 15 females) with a mean age of 50.4 years (range 26–65), who had normal ocular tension (NT), entered the study. There were no diabetics or systemic hypertensives in either group, and no subject was receiving medication, topical or systemic. Each gave written consent to participation, and the study was approved by the Ethics Committee of West Lambeth Health Authority.

METHODS

Recordings were made in duplicate with the subject standing and, after 15 minutes' rest, supine. Measurements of intraocular pressure and ocular pulse amplitude were obtained by pneumotonometry, performed after instillation of 0.4% benoxinate, linked to a Langham ocular blood flow system.²² Simultaneous recordings were made of heart rate by standard electrocardiogram (ECG) and mean systemic blood pressure (diastolic plus one-third of the pulse pressure) with a Takeda Medical UA-751 digital blood pressure meter.

STATISTICAL ANALYSIS

Comparisons between the two groups were made by the unpaired Student's *t* test for the following variables: pulsatile ocular blood flow, intra-ocular pressure, ocular pulse amplitude, heart rate, and mean blood pressure. Within-group comparisons were made for these variables in the erect and supine postures by the paired *t* test.

Results

No significant differences existed between values for the right and left eyes, so for clarity of

presentation tables and figures illustrate effects on the right eye only. The effects of postural changes on variables concerned with the calculation of pulsatile ocular blood flow are reported first. Values for both the normotensive and hypertensive groups are given (Table 1 – mean, with SEM).

Both groups showed a significant rise in IOP on lying down, though this was greater in the hypertensives (OH: 4.7 (0.6) mmHg, $p<0.0001$; and NT: 3.1 (0.4) mmHg, $p<0.0001$). Ocular pulse amplitude (PA) increased on lying down in the OH group (0.3 (0.1) mmHg, $p<0.05$) but not in the normal controls. Pulsatile ocular blood flow (POBF) was significantly reduced in the supine position in both ocular normotensives (NT: -121 (21) μ l/min, $p<0.0001$) and hypertensives (OH: -75 (16) μ l/min, $p<0.0002$).

Mean heart rate was significantly reduced in the supine position in both groups (OH: 16 (1.9) bpm, $p<0.0001$; and NT: 11 (1.6) bpm, $p<0.0001$). There was a significant fall in mean blood pressure in both groups on lying down (OH: 6.8 (2.0) mmHg, $p<0.0005$; and NT: 6.6 (2.0) mmHg, $p<0.004$).

COMPARISON BETWEEN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS

Table 2 compares the values between the two groups for both erect and supine positions. The two groups showed marked differences in mean intraocular pressure (erect: 6.4 mmHg, $p<0.0001$; and supine: 8.0 mmHg, $p<0.0001$). While there were differences in POBF between the normotensives and hypertensives, the values did not reach statistical significance. Fig 1 illustrates the fall in POBF which occurs in both groups associated with the supine rise in IOP.

Ocular pulse amplitude was greater in the OH group than the normals in both erect and supine positions, though the difference reached statistical significance only in the latter ($p<0.05$). These values are illustrated in Fig 2.

The ocular hypertensives had a higher mean heart rate than normals in both positions, but the difference was significant only when standing (erect: 11 bpm, $p<0.05$; supine: 6 bpm, $p=NS$). Similarly, mean blood pressure was higher in the OH group, but the differences failed to reach statistical significance.

Discussion

The technique of pneumotonometry has been available for some considerable time and the accuracy of recorded IOP measurements compared with a Goldmann 'standard' has been

Table 2 Differences between ocular normotensive and hypertensive subjects in ocular and systemic variables concerned in pulsatile ocular blood flow: mean (SEM)

Variable	Posture	Normotensives (N)	Hypertensives (H)	Mean difference (H - N)	p
Heart rate (bpm)	Erect	70 (1.5)	81 (3.5)	+11	<0.05
	Supine	59 (1.5)	65 (3.0)	+6	NS
Mean BP (mmHg)	Erect	97.4 (2.6)	104.9 (2.7)	+7.5	NS
	Supine	90.8 (2.9)	98.1 (2.1)	+7.3	NS
IOP (mmHg)	Erect	16.2 (0.7)	22.6 (0.6)	+6.4	<0.0001
	Supine	19.3 (0.7)	27.3 (0.7)	+8.0	<0.0001
Pulse amplitude (mmHg)	Erect	1.8 (0.2)	2.1 (0.1)	+0.3	NS
	Supine	1.8 (0.2)	2.4 (0.2)	+0.6	<0.05
POBF (μ l/min)	Erect	453 (46)	427 (26)	-26	NS
	Supine	332 (40)	352 (26)	+20	NS

NS=not significant.

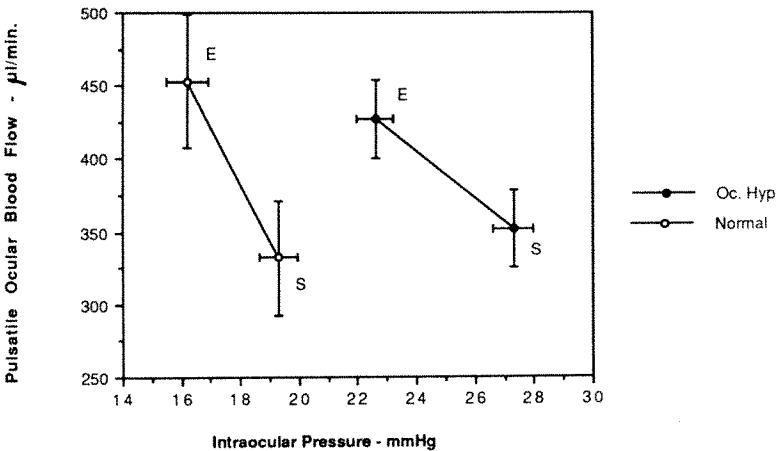


Figure 1: Relationship between mean intraocular pressure and pulsatile ocular blood flow in the right eye (n=20 normals; 18 ocular hypertensives). Vertical and horizontal lines indicate SEM. E=erect; S=supine.

established previously.²³ Our version of the Langham system uses a compressed air cylinder to deliver a constant gas flow to the hand-held pneumotonometer probe. Measurements are easy to perform, and the computer records values every 30 milliseconds over a five-second time period.

The variation of the IOP with the heart rate is presented by the computer in waveform (Fig 3) and allows the calculation of the pulse amplitude between systolic and diastolic intraocular pressures (the ocular pulse).²⁴ This pressure difference corresponds to an ocular volume change which occurs as a bolus of arterial blood enters the eye during systole.²⁵ Manometric studies, both in enucleated eyes and in living human eyes prior to enucleation, have correlated the volume changes produced by a given bolus to a measured pressure increase.^{26,27} At present it is unclear how the 'pressure-volume' relationship may be modified in eyes of different sizes. Recordings from myopic eyes tend to have a smaller pulse amplitude, and hypermetropic eyes the opposite.^{28,29} We are conducting a study to correlate pulse amplitude with axial length and refractive state of the eye.

The derived values obtained in this way are combined with two other parameters: first, the subject's heart rate and second, the duration of

the systolic and diastolic phases of the IOP pulse waveform. Calculation of the pulsatile component of ocular blood flow (POBF) is made from these data.²² It is emphasised that non-pulsatile flow is not measured by this technique, the calculations depending upon the IOP change produced by the entry of a bolus of arterial blood into the ocular circulation at systole. Doppler ultrasound studies of the ophthalmic artery have demonstrated a blood flow velocity during diastole,³⁰ suggesting the existence of a non-pulsatile component to total ocular blood flow. Furthermore, these authors report an increased diastolic blood flow velocity in the supine position. The extent to which these changes affect non-pulsatile flow and therefore the total amount of blood passing through the eye remains unclear at present.

In our studies pulsatile ocular blood flow showed a marked fall in the supine position in both groups, and this corresponded with the rise in intraocular pressure associated with lying down. Furthermore, our values of POBF in normals, when supine, are somewhat lower than those described by Hopkins³¹ in a smaller number of normotensive subjects, but the mean IOP of our normotensive group was about 3 mm Hg higher. No such association between POBF and IOP was found, however, when our two groups were compared. Although the ocular hypertensive group showed, as expected, higher mean pressures than normal, the pulsatile blood flow values were remarkably similar in the two groups, for both postures. This is an important observation as it implies that intraocular pressure is not the sole determinant of pulsatile ocular blood flow.

The pulse amplitude of IOP (the ocular pulse) is related to arterial pulsation and reflects the influx of blood into the eye with each heart beat;²⁸ the greater the pulse amplitude, the larger the bolus of blood entering the eye. The ocular hypertensives showed a slightly greater pulse amplitude than did the normotensives, which was less stable with a change in posture. Although this has been noted before, our values for both groups are much lower than those found by Perkins in his series.²⁹ As a group, the hypertensives were older, and an age related increase in scleral rigidity may well be expected to increase the pulse amplitude. However, in the same study Perkins found no correlation between age and pulse amplitude. Furthermore, another study by Friedman *et al* found that there were no significant age effects on the coefficient of scleral rigidity over the age of 60, though its participants were somewhat older than our study groups.³²

Mean blood pressure was higher in the ocular hypertensive group, in both positions. This may be of significance, as the perfusion pressure of the ocular vasculature is determined by the difference between mean ophthalmic arterial blood pressure and intraocular pressure; such postural changes in perfusion pressure have been recorded in other studies.^{33,34} In the presence of a raised intraocular pressure the arterial perfusion pressure (and therefore blood flow) may be maintained owing to an increase in mean blood pressure. Such an association may, however, be coincidental. Schulzer and Drance were unable

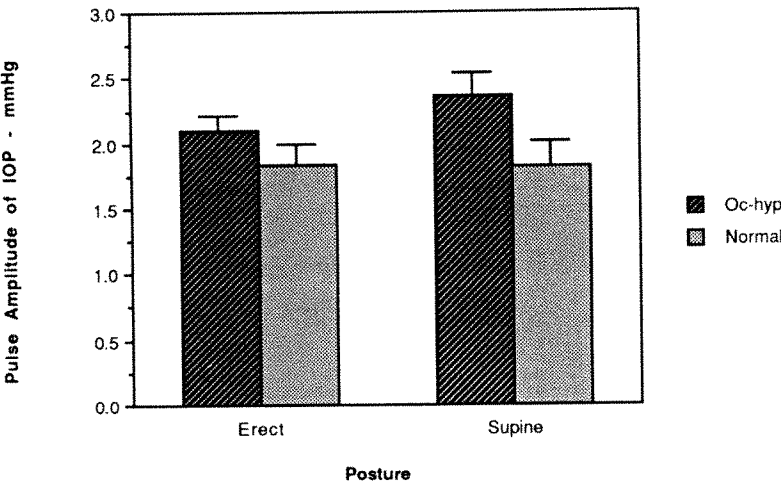


Figure 2: Postural changes in mean pulse amplitude of intraocular pressure. Vertical lines indicate SEM.

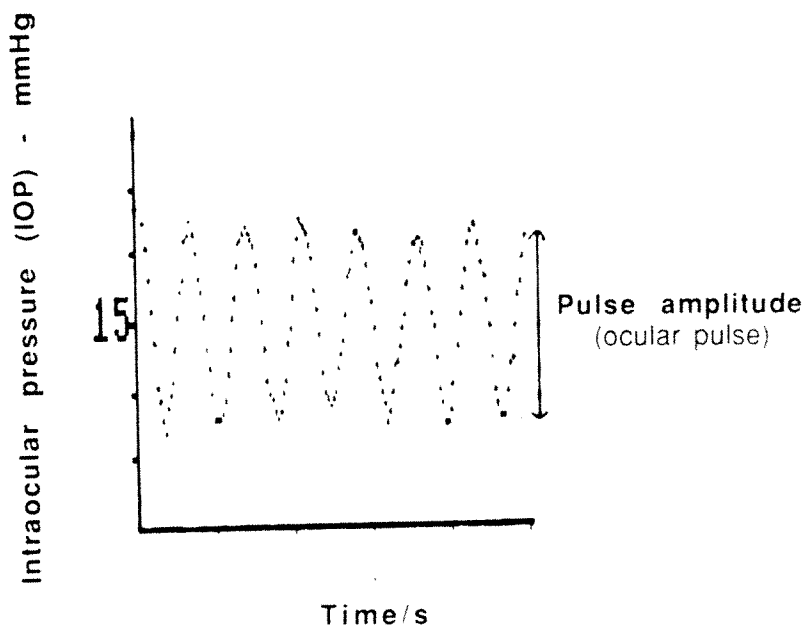


Figure 3: Variation of intraocular pressure with time – the ocular pulse.

to find a positive correlation between IOP and systolic blood pressure in a large group of subjects.³⁵ They found that any associations were age related, which in our study could just reflect the differences between groups.

The resting heart rate falls profoundly when the subject is supine, and this affects POBF, which represents a volume flow per minute. A significant difference was noted between the two groups, but despite the ocular hypertensives displaying a higher mean heart rate, the POBF in the two groups was the same whether standing or lying. These observations of differences in heart rate are important, as they provide another possible reason for the postural reduction in POBF, but again they do not explain the similarities noted between the groups. An alternative explanation might be, of course, that the OH patients are maintaining their blood flow because of their higher heart rate and blood pressure, and this is further discussed below.

From our results it can be seen that differences exist in several parameters between the two groups. These combine, however, to produce pulsatile components of ocular blood flow which are the same in both ocular normotensives and hypertensives. Furthermore, both groups show a similar postural fall of POBF on lying down, but the reasons for these observations remain unclear at present. Additional information may be obtained, however, by performing a derived analysis of the volume of blood in a single arterial pulse. The heart rate exerts a major influence on POBF, and rate changes are presumably responsible, at least in part, for the postural alterations in flow observed here. Division of the POBF ($\mu\text{l}/\text{min}$) by the heart rate (beats/min) gives us a value for this single arterial pulse volume (μl) which, interestingly, did not show a postural variation in the ocular hypertensive group (mean, SEM) (erect: 5.69 (0.35) μl , supine: 5.61 (0.4) μl). The normotensives did show a reduction in this value on lying down, although this was small (erect: 6.42 (0.65) μl , supine: 5.58 (0.6) μl $p < 0.05$). There was no significant difference between the groups.

Further investigation of the relative contribution of the heart rate to POBF and the possible determination of single arterial pulse volumes is clearly required. Investigations in this department are currently being performed on patients with cardiac pacemakers in which the heart rate can be set to a predetermined level, eliminating any postural variation and allowing closer scrutiny of POBF.

In conclusion, we have demonstrated a reduction in the pulsatile component of ocular blood flow, in both ocular normotensives and hypertensives, when they assume the supine posture from the upright. The mean values of POBF were similar in both groups despite the raised intraocular pressure of the hypertensives. A companion paper describes postural effects in a group of patients with chronic open angle glaucoma both with and without topical treatment.

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- Anderson DR, Grant WM. The influence of position on IOP. *Invest Ophthalmol Vis Sci* 1973; 12: 204–12.
- Galin MA, McIlvor JW, Magruder GB. Influence of position on intraocular pressure. *Am J Ophthalmol* 1963; 55: 720–3.
- Tarkkanen A, Leikola J. Postural variations of the intraocular pressure as measured with the Mackay-Marg tonometer. *Acta Ophthalmol (khh)* 1967; 45: 569–74.
- Tsukahara S, Sasaki T. Postural change in IOP in normal persons and in patients with primary wide open-angle and low-tension glaucoma. *Br J Ophthalmol* 1984; 68: 389–92.
- Leonard TJK, Kerr Muir MG, Kirkby GR, Hitchings RA. Ocular hypertension and posture. *Br J Ophthalmol* 1983; 67: 362–6.
- Sossi N, Anderson DR. Effect of elevated intraocular pressure on blood flow. Occurrence in cat optic nerve head studied with iodoantipyrine 1-125. *Arch Ophthalmol* 1983; 101: 98–101.
- Alm A, Bill A. Ocular and optic nerve blood flow at normal and increased intraocular pressures in monkeys (*Macaca irus*): a study with radioactively labelled microspheres including flow determinations in brain and some other tissues. *Exp Eye Res* 1973; 15: 15–29.
- Anderson DR. The posterior segment of glaucomatous eyes. *Basic aspects of glaucoma research*. Stuttgart: Schattauer. 1982: 167–90.
- Alm A, Bill A. The oxygen supply to the retina, II. Effects of high intraocular pressure and of increased arterial carbon dioxide tension on uveal and retinal blood flow in cats. A study with radioactively labelled microspheres including flow determinations in brain and some other tissues. *Acta Physiol Scand* 1972; 84: 306–19.
- Sperber GO, Bill A. Blood flow and glucose consumption in the optic nerve, retina and brain: effects of high intraocular pressure. *Exp Eye Res* 1985; 41: 639–53.
- Flower RW, Klein GJ. Pulsatile flow in the choroid: circulation: a preliminary investigation. *Eye* 1990; 4: 310–8.
- Hill DW, Pike ER, Gardner K. Laser Doppler velocimetry of the retinal blood flow. *Trans Ophthalmol Soc UK* 1981; 101: 152–5.
- Riva CE, Grunwald JE, Petrig BL, Sinclair SH. Blood velocity and volumetric flow rate in human retinal vessels. *Invest Ophthalmol Vis Sci* 1985; 26: 1124–32.
- Riva CE, Grunwald JE, Sinclair SH. Laser Doppler measurement of relative blood velocity in the human optic nerve head. *Invest Ophthalmol Vis Sci* 1982; 22: 241–8.
- Hickam JB, Frayser R. A photographic method for measuring the mean retinal circulation time using fluorescein. *Invest Ophthalmol Vis Sci* 1965; 4: 1129–36.
- Bulpiat C, Dollery CT. Estimation of retinal blood flow: measurement of the mean circulation time. *Cardiovasc Res* 1971; 5: 406–12.
- Nagasubramanian S, Perkins ES, Gloster J. Combined reflectometric and photographic study of the retinal and choroid circulation at raised intraocular pressure. *Trans Ophthalmol Soc UK* 1977; 97: 177–84.
- Richard G. Differentiation of retinal circulation times: videoangiography. *Ophthalmologica* 1985; 191: 161–8.
- Langham ME. Ocular blood flow and visual loss in glaucomatous eyes. In: Kriegstein GK, ed. *Glaucoma update 1*. Berlin: Springer, 1987: 58–66.
- Roy MS, Harrison KS, Harvey E, Mitchell T. Ocular blood flow in dogs using radiolabelled microspheres. *Int J Radiat Appl Instrum (B)* 1989; 16: 81–4.

- 21 Henkind P, Hansen RI, Szalay J. Ocular circulation. In: Duane TD, Jaeger EA, eds. *Biomedical foundations of ophthalmology II*. Philadelphia: Harper and Row, 1986: chapter 5: 1-54.
- 22 Langham ME, Farrell RA, O'Brien V, Silver DM, Schilder P. Blood flow in the human eye. *Acta Ophthalmol (khh)* 1989; 191 (suppl): 9-13.
- 23 Quigley HA, Langham ME. Comparative intraocular pressure measurements with the pneumotonograph and Goldmann tonometer. *Am J Ophthalmol* 1975; 80: 266-73.
- 24 Silver DM, Farrell RA, Langham ME, O'Brien V, Schilder P. Estimation of pulsatile ocular blood flow from intraocular pressure. *Acta Ophthalmol (khh)* 1989; 191 (suppl): 25-9.
- 25 Langham ME, To'mey KF. A clinical procedure for the measurements of the ocular pulse pressure relationship and the ocular arterial pressure. *Exp Eye Res* 1978; 27: 17-25.
- 26 Eisenlohr JE, Langham ME, Masumene AEW. Manometric studies of the pressure volume relationships in living and enucleated eyes of individual human subjects. *Br J Ophthalmol* 1962; 46: 536-48.
- 27 Langham ME, Eisenlohr JE. A manometric study of the rate of fall of the intraocular pressure in the living and dead eyes of human subjects. *Invest Ophthalmol Vis Sci* 1963; 2: 72-82.
- 28 Perkins ES. The ocular pulse and intraocular pressure as a screening test for carotid artery stenosis. *Br J Ophthalmol* 1985; 69: 676-80.
- 29 Perkins ES. The ocular pulse. *Curr Eye Res* 1981; 1: 19-23.
- 30 Canning CR, Restori M. Doppler ultrasound studies of the ophthalmic artery. *Eye* 1988; 2: 92-5.
- 31 Hopkins SD. Ocular haemodynamics in cataractous eyes. *Acta Ophthalmol (khh)* 1989; 191 (suppl) 43-8.
- 32 Friedman E, Ivry M, Ebert E, Glynn R, Gragoudas E, Seddon J. Increased scleral rigidity and age-related macular degeneration. *Ophthalmology* 1989; 96: 104-8.
- 33 Langham ME. Vascular pathophysiology of the ocular postural response. *Trans Ophthalmol Soc UK* 1975; 95: 281-7.
- 34 Hague S, Hill DW. Postural changes in perfusion pressure and retinal arteriolar calibre. *Br J Ophthalmol* 1988; 72: 253-7.
- 35 Schulzer M, Drance SM. Intraocular pressure, systemic blood pressure, and age: a correlational study. *Br J Ophthalmol* 1987; 71: 245-9.

FIFTY YEARS AGO

Eye Injuries in Air Raids

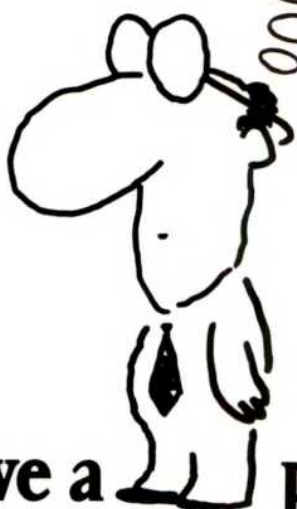
Ophthalmology has been called the Cinderella of Medicine and Surgery, left alone to fend for herself, often with meagre accommodation and equipment, in a general hospital. On December 29 [1940], the night of the severest incendiary raid on London to date, Cinderella was much in evidence with the cinders and was very much occupied long after midnight. At one large eye hospital in the City, 280 corneal and conjunctival foreign bodies were removed from members of the Fire Services between midnight and 5.30 a.m. Charred material formed the bulk of these foreign bodies. Most of the men had been attended to at First Aid Posts by the instillation of castor oil drops, had returned to their duties, been compelled to retire again on account of discomfort and then visited an eye surgeon. The first 100 to be treated all removed their pad and bandage on leaving the hospital to return to their duties of fire-fighting and so for the remainder this therapeutic refinement was dispensed with, thus affording a saving of time and material. The eye injuries caused by flying glass have been severe and on one night at a general hospital in the City the eye

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Annotation in *Br J Ophthalmol* 1941; 25: 179-80.

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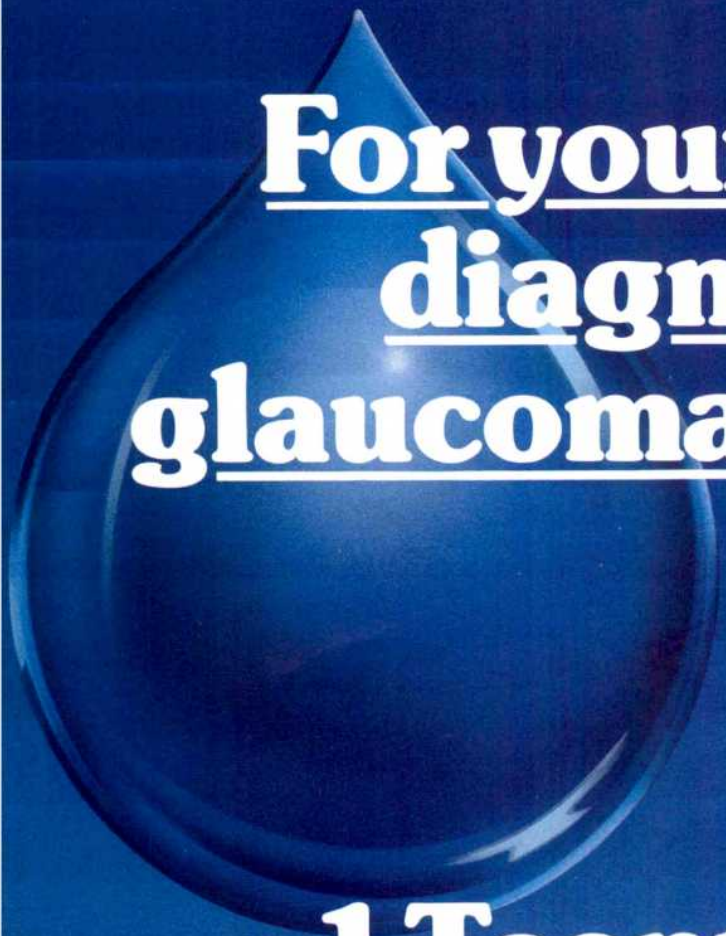
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¹Duzman, E. *et al.*, Am J Ophthalmol 1982; 94 (3): 318-327. ²Rakofsky S.I. *et al.*, Ophthalmology 1989; 96 (1): 8-11. ³Wandel, T. *et al.*, Am J Ophthalmol 1986; 101: 298-304.



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References

1. Maclure, G.M. et al. 3rd Congress of European Glaucoma Society, 1988.
2. Kitazawa, Y. et al. Acta XXIV International Congress of Ophthalmology, 1983. P. Henkind (Ed), Lippincott, Philadelphia.
3. Hugues, F.C. et al. J. Fr. Ophthalmol. 1987; **10**, 8/9, 485-490.
4. Negishi, C. Acta Soc. Ophthalmol. Jpn. 1982; **85**, 57-66.
5. Scoville, B. et al. American Journal of Ophthalmology, 1988; **105**, No.2, 150-154.

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Postural studies in pulsatile ocular blood flow: II. Chronic open angle glaucoma

D R Trew, S E Smith

Abstract

The pulsatile ocular blood flow (POBF) has been recorded in 15 patients with chronic open angle glaucoma. Measurements were performed during regular treatment with timolol 0.25% eyedrops, two weeks after withdrawal of this treatment, and then a further two weeks after its reinstitution. Readings were taken with subjects in both the erect and supine positions by means of a pneumotonometric probe to measure intraocular pressure (IOP), linked to a Langham ocular blood flow system. Assumption of the supine posture was associated with a significant increase in IOP in all phases of the study. Treatment with timolol lowered the mean IOP in comparison with the untreated phase (-4.4 (SEM 0.6) mmHg, $p < 0.001$) but had no effect on the postural change. A significant reduction in POBF was recorded on assumption of the supine posture (-66 (SEM 18) $\mu\text{l}/\text{min}$, $p < 0.001$), representing a mean decrement of 19%. However, there were no significant differences in POBF between treated and untreated phases of the study. Comparison of the values obtained in patients with glaucoma (COAG) after withdrawal of treatment with those in subjects with ocular hypertension revealed that there was no significant difference in intraocular pressure between the two groups. However, both POBF (-68 (SEM 29) $\mu\text{l}/\text{min}$) and the pulse amplitude of the intraocular pressure (ocular pulse: -0.45 (SEM) 0.14 mmHg) were significantly lower in the COAG patients. Pulsatile ocular blood flow is significantly lower in patients with chronic open angle glaucoma. Furthermore, the POBF and the postural response of these patients is not improved by the use of topical timolol therapy.

Standard treatments for chronic open angle glaucoma rely exclusively on the reduction of intraocular pressure (IOP). Despite apparent satisfactory pressure control, visual function declines progressively in a proportion of patients.¹⁻⁵ One possible explanation is that ocular blood flow is impaired in these patients, particularly when they are recumbent. We have described a significant reduction in pulsatile ocular blood flow (POBF) in ocular hypertensives and normotensives on assuming the supine posture from the upright.⁶ Intraocular pressure rises in the supine position,^{7,8} and this may lower perfusion pressure, which would eventually reduce blood flow.⁹ Furthermore, this postural response of the IOP is greater in ocular hypertensive¹⁰ and glaucoma subjects¹¹ and the effect is known to persist despite hypotensive treatment.^{12,13}

Photographic studies have shown that treatment with topical timolol reduces retinal arterial calibre.¹⁴ There is some evidence also, in rabbits, of a resultant reduction in blood flow,¹⁵ though the opposite has also been demonstrated in humans.¹⁶ These effects are thought to be mediated by a direct effect on vascular β -2 receptors¹⁷ irrespective of the hypotensive effect of timolol. These studies illustrate effects on retinal circulation, but this represents only a small percentage of total ocular blood flow, most of which passes through the ciliochoroidal system.^{18,19} They therefore take no account of the major blood supply via the posterior ciliary circulation, particularly to the optic nerve head. Although some workers consider vessels in this region to demonstrate autoregulation,²⁰⁻²² like that of the retinal vessels,^{9,23,24} it is difficult to substantiate, particularly as the rest of the choroidal system appears not to be autoregulated.²⁵ Interestingly, there has been some evidence from reflectometry and photography that intraocular pressure rises affect blood flow through the choroid in the peripapillary region significantly more than in the retinal circulation.²⁶

The pulsatile component of total ocular flow may be derived from measurements of intraocular pressure²⁷ by applanation pneumotonometry linked to a Langham ocular blood flow system.²⁸ In this study we have investigated the relationship of pulsatile ocular blood flow (POBF) to posture in patients with chronic open angle glaucoma receiving treatment with topical timolol 0.25%. Comparison has been made with a group of healthy ocular hypertensive subjects described in our companion paper.⁶

Subjects and methods

SUBJECTS

Fifteen patients, six male and nine female, with chronic open angle glaucoma (COAG) were recruited from the outpatients department. The mean age of the group was 67.4 years (range 42-78). Each was under treatment solely with topical timolol 0.25% twice daily and was receiving no systemic medication. There were no diabetics or systemic hypertensives in the group. Each gave written consent to participate, and the study was approved by the Ethics Committee of West Lambeth Health Authority.

STUDY DESIGN

The patients were studied on three occasions: (1) while receiving regular treatment with timolol 0.25% eyedrops; (2) two weeks after withdrawal of the treatment; and (3) a further

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two weeks after its reinstitution. The patients attended at the same time of day on each occasion.

METHODS

Measurements of intraocular pressure and ocular pulse amplitude were obtained by applanation pneumotonometry linked to a Langham ocular blood flow system, performed after instillation of 0.4% benoxinate. Simultaneous recordings were made of heart rate by standard electrocardiogram (ECG) and mean systemic blood pressure (diastolic plus one-third of the pulse pressure) with a Takeda Medical UA-751 Digital blood pressure meter. Measurements were performed in duplicate with the subject standing and, after 15 minutes' rest, supine.

Values of POBF were derived from the intraocular pressure pulse waveform and amplitude together with the heart rate, as described in the companion paper.⁶

STATISTICAL ANALYSIS

Postural and treatment effects on POBF, intraocular pressure, ocular pulse amplitude, heart rate, and mean blood pressure were compared by analysis of variance appropriate for an experiment of factorial design.²⁹ In the analysis of the following results no significant interaction was found for any of the recorded or calculated variables between patient groups and the postural changes observed. Similarly for the COAG patients no significant interactions were found between treatment (timolol) effects and the postural changes which occurred. In these comparisons, therefore, it is assumed that the postural effects are independent of patient groups and treatment, and they are reported as such. Comparisons of the same variables, between COAG patients off treatment and ocular hypertensives studied in our companion paper,⁶ were made in the same way.

Comparisons between the on-treatment phase and the retreatment phase in COAG patients for the above variables were made by Student's paired *t* test.

Results

There were no significant differences between values for the right and left eyes, so for clarity of presentation the tables and figures illustrate effects on the right eye only. There were no significant differences between patients receiv-

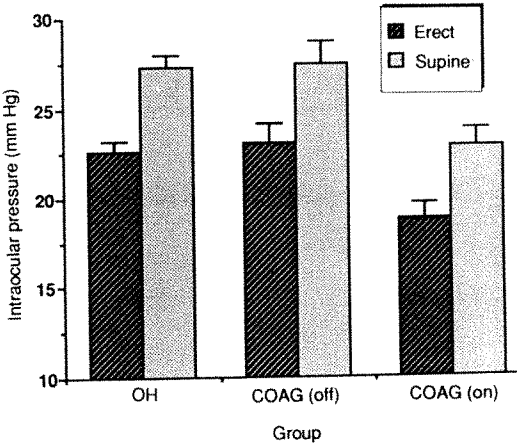


Figure 1 Effect of posture on mean intraocular pressure in the right eye. Groups shown: ocular hypertensives (OH), untreated (off) and treated (on) glaucoma patients. Vertical lines indicate SEM.

ing treatment with timolol eyedrops and having reinstituted treatment in the third phase of the study (Table 1). Comparisons are made therefore between treated and untreated phases.

Group mean values for IOP, ocular pulse amplitude, and POBF of ocular hypertensive subjects (from the companion study⁶) and of glaucoma patients off and on timolol treatment in erect and supine positions are shown in Figures 1, 2, and 3 respectively. The relationship between IOP and POBF in the glaucoma patients is illustrated in Figure 4.

COMPARISON BETWEEN COAG AND OCULAR HYPERTENSIVE PATIENTS

Group differences and postural effects are given in Table 2. By comparison with ocular hypertensives, COAG patients had a significantly reduced ocular pulse amplitude ($p<0.01$) and POBF ($p<0.05$) without difference in heart rate, mean blood pressure, or IOP. Assumption of the supine position was associated with a significant fall in heart rate ($p<0.001$), a rise in IOP ($p<0.001$), and a reduction in POBF ($p<0.05$) without change in mean blood pressure or ocular pulse amplitude. The lack of statistical interaction (see above) indicates that the postural changes did not differ between the patient groups.

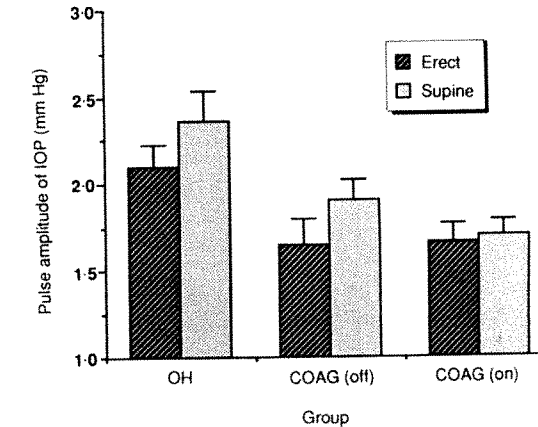


Figure 2 Effect of posture on the mean pulse amplitude of intraocular pressure in the right eye. Symbols as for Figure 1.

Table 1 Differences between treated and retreated phases, in COAG patients, in ocular and systemic variables concerned in pulsatile ocular blood flow: mean (SEM)

Variable	Posture	Treated	Retreated	Mean difference	p
Heart rate (bpm)	Erect	73.8 (3.5)	72.9 (2.5)	0.9	NS
	Supine	64.8 (2.9)	66.9 (2.1)	2.1	NS
Mean BP (mmHg)	Erect	104.8 (3.7)	103.6 (4.3)	1.2	NS
	Supine	97.1 (3.5)	95.1 (3.3)	2.0	NS
IOP (mmHg)	Erect	18.8 (0.9)	17.8 (0.9)	1.0	NS
	Supine	22.9 (1.0)	21.7 (0.9)	1.2	NS
Pulse amplitude (mmHg)	Erect	1.7 (0.1)	1.7 (0.1)	0	NS
	Supine	1.7 (0.1)	1.7 (0.1)	0	NS
POBF (µl/min)	Erect	365 (29)	389 (32)	24	NS
	Supine	287 (25)	310 (25)	23	NS

NS=not significant.

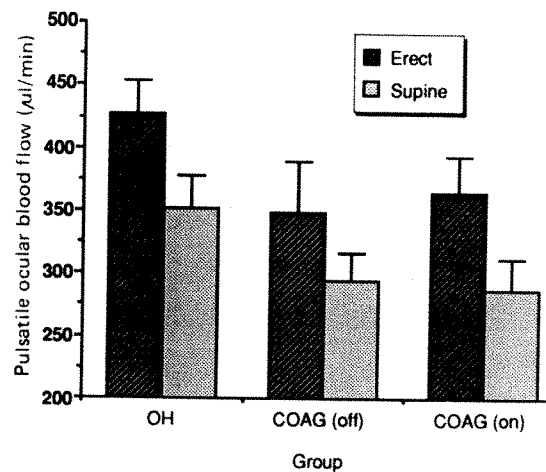


Figure 3 Effect of posture on the mean pulsatile ocular blood flow in the right eye. Symbols as for Figure 1.

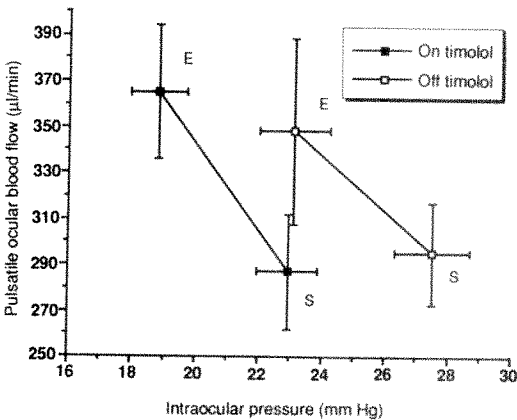


Figure 4 Effect of intraocular pressure on mean pulsatile ocular blood flow in the right eye of glaucoma patients when on and off timolol treatment. Vertical and horizontal lines indicate SEM. E=erect. S=supine.

EFFECTS OF TIMOLOL TREATMENT

Treatment and postural effects in COAG patients are given in Table 3. Timolol significantly reduced heart rate ($p<0.001$) and IOP ($p<0.001$) but did not alter mean blood pressure, ocular pulse amplitude, or POBF. In these subjects assumption of the supine position significantly reduced heart rate ($p<0.001$) and mean blood pressure ($p<0.01$), caused a rise in IOP ($p<0.01$) and a reduction in POBF ($p<0.001$), but was without effect on ocular pulse amplitude. The lack of statistical interaction (see above) indicates that timolol treatment did not alter the ocular or systemic responses to postural change.

RESPONSES OF INDIVIDUAL PATIENTS

Figure 5 shows the responses of intraocular pressure to drug treatment. It demonstrates that in many patients IOP was lowered close to, if not within, the normal range. Individual patient results for changes in pulsatile ocular blood flow are illustrated in Figure 6 and provide a contrast to the IOP findings. In the supine posture, when POBF values are at a minimum, timolol

markedly reduced flow still further in two of the 15 patients. In one of these the flow was reduced by 44% and in the other by 40%. In addition three further patients in this group had persistently low values of POBF which failed to change in response to drug treatment.

Discussion

Two important matters emerge from these observations. First, pulsatile ocular blood flow is significantly lower in patients with chronic open angle glaucoma than in subjects with ocular hypertension. Secondly pulsatile ocular blood flow and the postural response of these patients are not improved by the use of topical timolol therapy despite the resulting fall in IOP.

The general pattern of observations made on the glaucoma patients is similar to that made in healthy ocular normotensive and hypertensive subjects and illustrated in our companion paper.⁶ Assumption of the supine posture was associated with a rise in IOP in all phases of the study. Timolol treatment lowers the IOP in both postures, but it does not alter the postural change, as stated above. Similar observations have been made previously in ocular normotensives and glaucoma patients after instillation of topical β -blockers.^{12,13} Our patients received Ethics Committee approval for treatment withdrawal for a period of two weeks prior to measurement in the 'untreated' phase of the study. We recognise that this study design was not ideal, as some residual treatment effects may persist after this period of time.³⁰ Despite this, however, our results have demonstrated significant changes following treatment withdrawal, and any remaining effects would be small and unlikely to affect the validity of the overall results.

At the same time our COAG patients had a decreased POBF on lying down, as did subjects with ocular hypertension. The values for mean blood pressure followed a similar pattern. However, timolol treatment did not change POBF in either posture nor did it alter the postural change. In the glaucoma patients this would indicate that taken as a group, institution of timolol treatment, while reducing IOP, does not improve ocular perfusion. Similar findings have been suggested in other studies on vascular

Table 2 Comparison between untreated COAG patients and ocular hypertensive (OH) subjects and postural effects on ocular and systemic variables concerned with pulsatile ocular blood flow

Variable	Group comparison (COAG-OH)				Postural effect (lying-standing)			
	Mean	SEM	t	p	Mean	SEM	t	p
Heart rate (bpm)	1.8	3.6	0.516	NS	-14.7	3.6	-4.041	<0.001
Mean BP (mmHg)	0.2	3.0	0.070	NS	-5.4	3.0	-1.089	NS
IOP (mmHg)	0.3	0.9	0.344	NS	4.6	0.9	5.091	<0.001
Pulse amplitude (mmHg)	-0.45	0.14	-3.197	<0.01	0.26	0.14	1.802	NS
POBF (µl/min)	-68	29	-2.296	<0.05	-65	29	-2.226	<0.05

NS=not significant.

Table 3 Differences between treated (a) and untreated (b) COAG patients and postural effects on ocular and systemic variables concerned with pulsatile ocular blood flow

Variable	Treatment effect (a-b)				Postural effect (lying-standing)			
	Mean	SEM	t	p	Mean	SEM	t	p
Heart rate (bpm)	-6.7	1.6	-4.042	<0.001	-11.5	1.6	-6.994	<0.001
Mean BP (mmHg)	-0.9	1.7	-0.506	NS	-5.7	1.7	-3.388	<0.01
IOP (mmHg)	-4.4	0.6	-7.234	<0.001	4.2	0.6	6.907	<0.01
Pulse amplitude (mmHg)	-0.09	0.08	-1.134	NS	0.15	0.08	1.793	NS
POBF (µl/min)	5	18	0.253	NS	-66	18	-3.588	<0.001

NS=not significant.

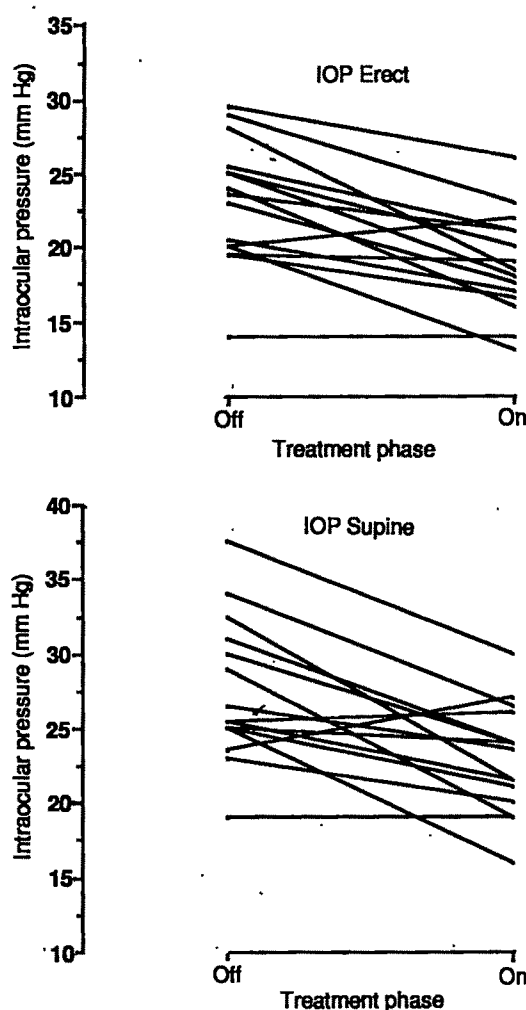


Figure 5 Changes in intraocular pressure for the right eye of individual glaucoma subjects when off and on timolol treatment. Above: erect. Below: supine.

parameters in timolol treated subjects.^{31,32} This observation is interesting because it suggests that the general vascular responses to this drug, such as a decreased heart rate and a reduction in blood pressure, may counteract the benefits accruing from its ocular hypotensive action.

Inspection of the data from individual patients showed that timolol adversely affected POBF in two of 15 patients in the supine posture. This reduction in blood flow may have important consequences not only for the perfusion of the optic nerve head but also for the outer layers of the retina, which are supplied via the choroidal circulation and which have such high metabolic requirements.

These observations have shown that the POBF and the postural response of glaucoma subjects were not improved by the use of topical timolol therapy. In some cases the values worsened in the supine position in comparison with the untreated phase. This may provide a basis for understanding the mechanisms underlying treatment failure in this type of patient, such as peripheral vasoconstriction locally, or reduction in heart rate systemically. Further prospective studies are required to confirm this finding and to relate it to long term changes in visual field defects. These observations suggest that research is needed into treatments which may by one mechanism or another improve blood flow to the diseased eye.

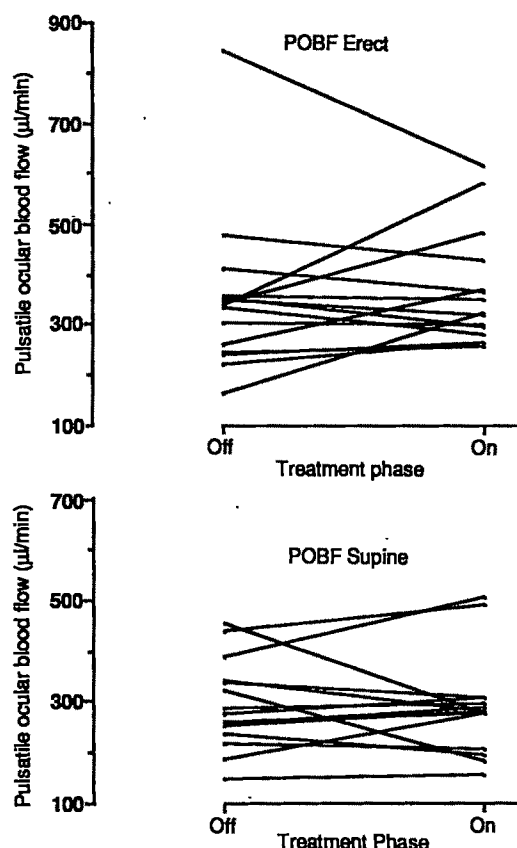


Figure 6 Changes in pulsatile ocular blood flow for the right eye of individual glaucoma subjects when off and on timolol treatment. Above: erect. Below: supine.

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- Schulzer M, Mikelberg FS, Drance SM. Some observations on the relation between intraocular pressure reduction and the progression of glaucomatous visual loss. *Br J Ophthalmol* 1987; 71: 486-8.
- Flammer J, Drance SM. The effect of glaucoma medications on the differential light threshold. *Doc Ophthalmol Proc Ser* 1983; 35: 146-8.
- Flammer J, Drance SM. Influence of pindolol and timolol treatment on the visual fields of glaucoma patients. *J Ocul Pharmacol* 1986; 2: 305-11.
- Smith RJH. The Lang Lecture 1986. The enigma of primary open-angle glaucoma. *Trans Ophthalmol Soc UK* 1986; 105: 618-33.
- Kidd MN, O'Connor M. Progression of field loss after trabeculectomy: a five-year follow-up. *Br J Ophthalmol* 1985; 69: 827-31.
- Trew DR, Smith SE. Postural studies in pulsatile ocular blood flow: I. Ocular hypertension and normotension. *Br J Ophthalmol* 1991; 75: 66-70.
- Galín MA, McIvor JW, Magruder GB. Influence of position on intraocular pressure. *Am J Ophthalmol* 1963; 55: 720-3.
- Anderson DR, Grant WM. The influence of position on IOP. *Invest Ophthalmol Vis Sci* 1973; 12: 204-12.
- Ffytche TJ, Bulpiatt CJ, Kohner EM, Archer D, Dollery CT. Effect of changes in intraocular pressure on the retinal microcirculation. *Br J Ophthalmol* 1974; 58: 514-22.
- Leonard TJK, Kerr Muir MG, Kirkby GR, Hitchings RA. Ocular hypertension and posture. *Br J Ophthalmol* 1983; 67: 362-6.
- Tsukahara S, Sasaki T. Postural change of IOP in normal persons and in patients with primary wide open-angle glaucoma and low-tension glaucoma. *Br J Ophthalmol* 1984; 68: 389-92.
- Smith DA, Trope GE. Effect of beta-blockers on altered body position induced ocular hypertension. *Invest Ophthalmol Vis Sci* 1989; 26: ARVO.
- Parsley J, Powel RG, Keightley SJ, Elkington AR. Postural response of intraocular pressure in chronic open-angle glaucoma following trabeculectomy. *Br J Ophthalmol* 1987; 71: 494-6.
- Martin XD, Rabineau PA. Vasoconstrictive effect of topical timolol on human retinal arteries. *Graefes Arch Clin Exp Ophthalmol* 1989; 27: 526-30.
- Yan H-Y, Chiou GCY. Effects of L-timolol, D-timolol, haloperidol and domperidone on rabbit retinal blood flow

- measured with laser Doppler method. *Ophthalmic Res* 1987; **19**: 45-8.
- 16 Grunwald JE. Effect of topical timolol on the human retinal circulation. *Invest Ophthalmol Vis Sci* 1986; **27**: 1713-9.
- 17 Ferrari-Dileo G. Beta₁ and beta₂ adrenergic binding sites in bovine retina and retinal blood vessels. *Invest Ophthalmol Vis Sci* 1988; **29**: 695-701.
- 18 Langham ME. Ocular blood flow and visual loss in glaucomatous eyes. In: Kriegelstein GK, ed. *Glaucoma update III*. Berlin, Heidelberg: Springer, 1987: 58-66.
- 19 Roy MS, Harrison KS, Harvey E, Mitchell T. Ocular blood flow in dogs using radiolabelled microspheres. *Int J Radiat Appl Instrum (B)* 1989; **16**: 81-4.
- 20 Anderson DR. The posterior segment of glaucomatous eyes. *Basic aspects of glaucoma research*. Stuttgart: Schattauer, 1982: 167-90.
- 21 Sossi N, Anderson DR. Effect of elevated intraocular pressure on blood flow. Occurrence in cat optic nerve head studied with iodoantipyrine I-125. *Arch Ophthalmol* 1983; **101**: 98-101.
- 22 Alm A. Microspheres in optic nerve blood flow measurements. In: Lambrou GN, Greve EL, eds. *Ocular blood flow in glaucoma*. Amsterdam: Kugler and Ghedini, 1989: 65-8.
- 23 Riva CE, Grunwald JE, Petrig BL. Autoregulation of human retinal blood flow. An investigation with laser Doppler velocimetry. *Invest Ophthalmol Vis Sci* 1986; **27**: 1706-12.
- 24 Stefansson E, Wagner HG, Seida M. Retinal blood flow and its autoregulation measured by intraocular hydrogen clearance. *Exp Eye Res* 1988; **47**: 669-78.
- 25 Bill A, Sperber GO. Control of retinal and choroidal blood flow. *Eye* 1990; **4**: 319-25.
- 26 Nagasubramian S, Perkins ES, Gloster J. Combined reflectometric and photographic study of the retinal and choroidal circulation at raised intraocular pressure. *Trans Ophthalmol Soc UK* 1977; **97**: 177-84.
- 27 Silver DM, Farrell RA, Langham ME, O'Brien V, Schilder P. Estimation of pulsatile ocular blood flow from intraocular pressure. *Acta Ophthalmol (Kbh)* 1989; **67** (suppl 191): 25-9.
- 28 Langham ME, Farrell RA, O'Brien V, Silver DM, Schilder P. Blood flow in the human eye. *Acta Ophthalmol (Kbh)* 1989; **67** (suppl 191): 9-12.
- 29 Snedecor GW, Cochran WG. Analysis of factorial experiments. *Statistical methods*. 6th ed. Iowa State University Press: Ames, 1967.
- 30 Schlecht LP, Brubaker RF. The effects of withdrawal of timolol in chronically treated glaucoma patients. *Ophthalmology* 1988; **95**: 1212-6.
- 31 Pillunat L, Stodtmeister R. Effect of different antiglaucomatous drugs on ocular perfusion pressures. *J Ocul Pharmacol* 1988; **4**: 231-42.
- 32 Grunwald JE, Furubayashi C. Effect of topical timolol maleate on the ophthalmic artery blood pressure. *Invest Ophthalmol Vis Sci* 1989; **30**: 1095-100.

Seroprevalence of antibodies to HTLV-I in patients with ocular disorders

Kumimko Nakao, Makoto Matsumoto, Norio Ohba

Abstract

Human T-lymphotropic virus type 1 (HTLV-I) has been shown to spread worldwide and to be responsible for distinct systemic diseases, namely adult T-cell leukaemia and HTLV-I-associated myelopathy. Immune-mediated, inflammatory lesions in the lungs, joints, and lacrimal glands (Sjögren's syndrome) are also suggested to be associated with the retrovirus. We studied seroprevalence of antibodies to HTLV-I in patients with various ocular disorders who are residents of south-west Japan, one of the endemic areas of HTLV-I. Of 310 patients with ocular disease 72 (23.2%) were seropositive. This seroprevalence did not differ significantly from that of the general population of the area. As regards individual ocular diseases, aetiologically undefined non-specific uveitis showed a significantly high seropositivity for HTLV-I. Of 44 patients 18 (40.9%) were seropositive. Their clinical features were acute or subacute, transient and sometimes recurrent, and granulomatous changes in the anterior uvea. Patients with isolated cotton-wool spot of the retina, non-familial retinitis pigmentosa, or keratoconjunctivitis sicca did not show any significantly high prevalence of HTLV-I infection.

Human T-lymphotropic virus type 1 (HTLV-I) is a recently defined retrovirus that may cause malignant disease of the blood (adult T-cell leukaemia),¹⁻³ and chronic neurological disease (HTLV-I-associated myelopathy or tropical spastic paraparesis).^{4,5} More recent studies also indicate that a diverse group of aetiologically unknown clinical disorders are probably associated with HTLV-I infection as well, including pulmonary alveolitis, Sjögren's syndrome, and arthropathy.⁵⁻⁸

HTLV-I has nothing to do with acquired immunodeficiency syndrome (AIDS), caused by a separate retrovirus HIV/HTLV-III,⁹ but has received much attention by many researchers. HTLV-I infection is worldwide, with endemic areas in south-west Japan, the Caribbean basin, central Africa, and Melanesia, and its main transmission routes include vertical transmission from infected mother to child, transfusion of infected blood, and sexual transmission.^{5,8}

Ocular disorders in patients with HTLV-I-associated systemic diseases include intraocular opportunistic infections such as cytomegalovirus retinitis in immunocompromised patients with adult T-cell leukaemia,^{10,11} and non-infectious anterior uveitis, microvascular changes of the retina, and retinochoroidal atrophic lesions in patients with HTLV-I-associated myelopathy.¹¹⁻¹⁵

Our hospital is located in south-west Japan, where HTLV-I infection is highly endemic, and we see many patients infected with the retrovirus. We have therefore performed a prospective study of HTLV-I seroprevalence in patients with various ocular diseases. The main purpose of this study was to search for any ocular disorder with an unusually high seroprevalence of HTLV-I infection.

Materials and methods

A series of 310 patients, 158 men and 152 women, whose age ranged from 10 to 83 years (mean, 54.7, SD 17.3), were the subjects of a prospective study for HTLV-I infection. They were residents of Kagoshima prefecture of south-west Japan, and presented with various ocular diagnoses during a three-year period 1987-9 (Table 1). Infection with HTLV-I was examined by assessment of serum antibodies against HTLV-I by the method of particle agglutination (PA method) as described elsewhere.¹⁰ Agglutination reaction in serum of over 16 times dilution was regarded as seropositive, hence infected with the retrovirus. The patients also received a thorough ophthalmic and systemic examination.

The prevalence of HTLV-I infection in the general population of south-west Japan was studied by the PA method in a control group of 2484 adults - 868 men and 1616 women, whose age ranged from 20 to 80 years (mean 55.4, SD 10.7).

The western blotting method (WB method) was also carried out on part of the material to confirm the accuracy of detection of the HTLV-I antibodies. Occasional materials showed inconsistency between the PA and the WB methods, though it was not so marked as to affect the conclusion in the present study.

The Mantel-Haenszel χ^2 test¹⁶ was used for statistical comparison between ocular diseases and general population in consideration of the age factor.

Results

Table 1 shows HTLV-I seroprevalence in patients with various ocular diseases, together with that in control adult residents of south-west Japan. Of 310 ophthalmic patients 72 (23.2%) were found to be infected with HTLV-I, the prevalence becoming higher with age. These results were compared with those for the general population of the same area, among whom 552 (22.2%) of 2484 control individuals were seropositive for HTLV-I, also with an increasingly high seropositivity with age. There was no significant difference in HTLV-I seroprevalence

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Table 1 Seroprevalence of antibodies to HTLV-I in various ocular disease

Ocular disease	Age (years):	Seroprevalence (seropositive cases/total cases)							
		10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89
Specific uveitis entities		0/3	0/8	2/9	1/10	5/13	2/10	1/1	
Ocular sarcoidosis		0/2	0/4		1/3	1/3	1/2	1/1	
Harada's uveomeningitis			0/2	0/3	0/4	3/5	0/5		
Behçet's disease				1/2	0/2	1/2			
Posner-Schlossman syndrome			0/1	0/1		0/1			
Ocular toxoplasmosis			0/1	1/3	0/1		1/1		
Fuchs's heterochromic cyclitis						0/2	0/1		
Herpetic uveitis		0/1					0/1		
Non-specific uveitis		1/4	1/4	4/7	1/3	4/8	4/10	1/6	2/2
Isolated cotton-wool spot			0/1		0/1	0/1	1/4	0/4	
Retinal vascular occlusion			0/1	0/1	0/1		0/1	0/1	1/2
Senile macular degeneration					0/2	1/1	1/8	3/6	0/1
Retinitis pigmentosa			0/1	1/3	1/9	0/4	4/10	2/4	0/1
Diabetic retinopathy					0/1	0/4	0/5	2/5	
Keratoconjunctivitis sicca				1/3	1/5	0/8	2/9		0/1
Pterygium					0/1	0/5	0/4	1/1	
Senile cataract					0/3	0/4	1/8	7/12	2/8
Miscellaneous		0/6	0/3	0/8	1/6	4/14	5/14	1/6	
Total		1/13	1/18	8/31	5/42	14/62	20/83	18/46	5/15
General population seroprevalence (%) of HTLV-I			3/21 (14.3%)	16/135 (11.9%)	110/614 (17.9%)	189/878 (21.5%)	172/646 (26.6%)	57/175 (32.6%)	5/15 (33.3%)
									22.2%

*Statistically significant $p < 0.01$ with the Mantel-Haenszel χ^2 test. Others are not significant in comparison with general population.

between the ophthalmic group and the general population (Fig 1). But a group of ocular diseases were specially prevalent among those associated with HTLV-I infection and warrant discussion.

As regards endogenous uveitis, 11 (20.4%) of 54 patients with specific clinical entities, including Behçet's disease and Harada's uveomeningitis, were infected with HTLV-I. However, this prevalence was not significantly higher than in the control population; this excludes any causative association with the retrovirus, though it might affect the clinical picture of ocular disease. On the other hand 18 (40.9%) of 44 patients with non-specific, aetiologically undefined uveitis showed infection with HTLV-I. This prevalence was significantly higher than in the control group ($\chi^2 = 7.62$, $df = 1$, $p < 0.01$), by the Mantel-Haenszel χ^2 test¹⁶ applied in consideration of the age-dependent increase of seroprevalence.

It is noticeable that non-specific uveitis in HTLV-I-infected patients was characterised by acute or subacute, mild granulomatous reactions in the anterior uveal tissue, such as Koeppe nodules and mutton-fat keratic precipitates with or without vitreous opacities, and that the disease subsided in a few weeks in an apparent response to local or systemic corticosteroids. Two of 18 such patients showed recurrent uveal reactions. All these HTLV-I-infected patients with characteristic uveitis remained otherwise normal in physical and laboratory studies during up to three years' follow-up. Case reports of some of these patients are given

elsewhere.¹² The following is an additional representative case.

CASE REPORT

A 32-year-old man complained of acute blurring of vision in the left eye. The corrected visual acuity was 20/20 in the right eye and 20/40 in the left eye. Slit-lamp examination revealed in the left eye granulomatous uveitis, showing 1+ cells in the anterior chamber, 2+ mutton fat keratic precipitates, and granular vitreous opacities. Four weeks' topical and systemic corticosteroid therapy brought about diminution of the inflammatory signs, and the visual acuity returned to 20/20. The patient remained normal in systemic and laboratory studies throughout the follow-up period of two years except for a seropositivity for HTLV-I.

Of 11 patients who showed isolated, asymptomatic cotton-wool spots or mild retinal microvasculopathy but had no accountable local or systemic disease one was found to be infected with HTLV-I.

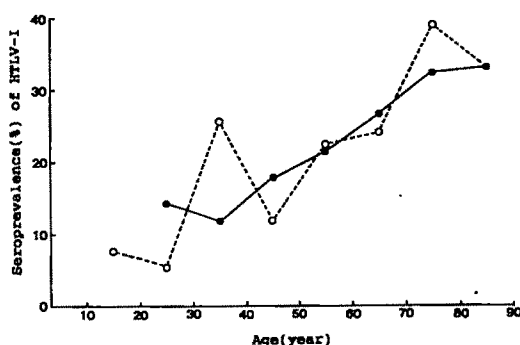
Of 32 patients with non-familial, isolated retinitis pigmentosa, eight (25.0%) had serum antibodies to HTLV-I, thus indicating no significant increase in HTLV-I seroprevalence over the control group.

As regards keratoconjunctivitis sicca, four (15.4%) of 26 patients showed HTLV-I infection, representing no significant increase in HTLV-I prevalence.

Discussion

The prevalence of HTLV-I infection is strikingly high in south-west Japan. Yet the majority of infected adults remain carriers without any overt clinical disease, as epidemiological studies indicate that only one in 1000-2000 infected individuals may suffer from malignant disease of blood or chronic neurological disease.¹⁷ In any case we should be cautious in interpreting the high seroprevalence in ocular diseases in terms of the virus's causative role. Indeed most of the ocular diseases studied here showed no statistically significant increase in prevalence over the

Figure 1 Seroprevalence of antibody to HTLV-I in a general population (closed circles: $n = 2484$) and patients with various ocular disorders (open circles: $n = 310$) plotted against age in years.



control population. Some comments may, however, deserve mention on a certain group of ocular disorders.

HTLV-I infection has received particular attention in recent years because, in addition to obvious systemic diseases (adult T-cell, leukaemia and HTLV-I-associated myelopathy), various aetiologically unknown disorders such as pulmonary alveolitis, arthropathy, Sjögren's syndrome, and myositis have been suggested to be involved in HTLV-I infection. A probable mechanism is thought to reside in immune mediated tissue reactions through polyclonal activation of T and B cell functions.^{3,8} In this connection the present observations appear of substantial interest, in that patients with aetiologically undefined, non-specific uveitis showed a significantly high seroprevalence of HTLV-I, and that the clinical features had an acute or subacute onset, consisted of granulomatous lesions in the anterior uvea, responded to local and/or systemic corticosteroid, and possibly ran a recurrent course. It is also emphasised that these patients remained otherwise intact in physical and laboratory studies. In particular we have found similar uveal disease in patients who had HTLV-I-associated myelopathy.^{11,12} It would therefore be plausible that uveal inflammatory disease should occur as an isolated form in close association with HTLV-I infection, and we are inclined to hypothesise HTLV-I-associated uveitis (HAU), though its pathogenesis remains to be defined.

Isolated cotton-wool spots or microvascular changes of the retina are seen in some patients with HTLV-I-associated myelopathy.^{11,14} In the present study we focused our attention on those patients who showed such retinal changes but did not show any accountable local or systemic disorder. One of nine such patients were found to be infected with HTLV-I. Further studies are justified to explore whether an isolated form of retinal microangiopathy is associated with HTLV-I infection.

We previously reported four cases of retino-choroidal degenerative changes which were found in 36 patients with HTLV-I-associated myelopathy, and discussed whether those cases represented a causative rather than a fortuitous association with HTLV-I infection, though the mechanism remained undefined.¹³ The observations prompted us to examine HTLV-I seroprevalence in those patients who had isolated, aetiologically unknown, non-familial retino-

choroidal degeneration (retinitis pigmentosa): and as a result eight of 32 cases were found to be infected with the retrovirus. This degree of seroprevalence does not differ from that in the general population, but the finding may neither upset nor support a hypothesis that HTLV-I infection may involve retinochoroidal changes phenotypically similar to hereditary disease.

Infection with HTLV-I is now recognised to be worldwide.^{3,8} Ophthalmologists should be aware of this newly defined retrovirus as well as another retrovirus human immunodeficiency virus (HIV/HTLV-III) causing acquired immunodeficiency syndrome.⁹

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- 1 Uchiyama T, Yodoi J, Sagawa K, Takatsuki K, Uchino H. Adult T-cell leukemia: Clinical and hematologic features of 16 cases. *Blood* 1977; 50: 481-92.
- 2 Hinuma Y, Nagata K, Hanaoka M, et al. Antigen in an ATL cell line and detection of antibodies to the antigen in human sera. *Proc Natl Acad Sci USA* 1981; 78: 6476-80.
- 3 Yoshida M, Miyoshi I, Hinuma Y. Isolation and characterization of retrovirus from cell lines of human adult T-cell leukemia and its implication in the disease. *Proc Natl Acad Sci USA* 1982; 79: 2031-5.
- 4 Osame M, Matsumoto M, Usuku K, et al. Chronic progressive myelopathy associated with elevated antibodies to HTLV-I and adult T-cell leukemia-like cells. *Ann Neurol* 1987; 21: 117-22.
- 5 Román GC, Vernant TC, Osame M. *HTLV-I and the nervous system*. New York: Liss, 1989.
- 6 Vernant JC, Buisson G, Magdeleine J, et al. T-lymphocyte alveolitis, tropical spastic paraparesis, and Sjögren syndrome. *Lancet* 1988; i: 177.
- 7 Maruyama M, Sakashita I. HTLV-I associated bronchopneumopathy - a new clinical entity. *Am Rev Resp Dis* 1989; 137: 46.
- 8 World Health Organisation. *Report of Scientific group on HTLV-I infections and associated diseases*. Manila, Philippines: World Health Organisation Regional Office for the Western Pacific, March 1989.
- 9 Shuman JS, Orellana J, Friedman AH, et al. Acquired immunodeficiency syndrome (AIDS). *Surv Ophthalmol* 1988; 31: 384-410.
- 10 Kabayama Y, Isashiki M, Uehara F, Ohba N. Ocular disorders associated with adult T-cell leukemia. *Rinsho Ganka (Jpn J Clin Ophthalmol)* 1988; 42: 139-41.
- 11 Ohba N, Matsumoto M, Samehima M, et al. Ocular manifestations in patients infected with human T-lymphotropic virus type 1 (HTLV-I). *Jpn J Ophthalmol* 1989; 33: 1-12.
- 12 Nakao K, Ohba N, Matsumoto M. Noninfectious anterior uveitis in patients infected with human T-lymphotropic virus type 1. *Jpn J Ophthalmol* 1989; 33: 472-81.
- 13 Nakao K, Ohba N, Isashiki M, et al. Pigmentary retinal degeneration in patients with HTLV-I-associated myelopathy. *Jpn J Ophthalmol* 1989; 33: 383-91.
- 14 Nakao K, Uemura A, Hirashima S, Unoki K. Cotton-wool spots on the retina in patients infected with human T-lymphotropic virus type 1 (HTLV-I). *Folia Ophthalmol Jpn* 1989; 40: 2051-7.
- 15 Sasaki K, Morooka I, Inomata H, Kashio N, Akamine T, Osame M. Retinal vasculitis in human T-lymphotropic virus type 1 associated myelopathy. *Br J Ophthalmol* 1989; 73: 812-5.
- 16 Kirkwood BR. *Essentials of medical statistics*. Oxford: Blackwell, 1988.
- 17 Tajima K, Tominaga S, Suchi T. Epidemiological analysis of the distribution of antibody to adult T-cell leukemia-virus-associated antigen: possible horizontal transmission of adult T-cell virus. *Jpn J Cancer Res* 1982; 73: 893-901.

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- REFERENCES:** 1 Jones FL, Ekberg NL, Letter N Eng J Med 1979; **301**: 270
2 Levy NS, Boone L, Ellis E. Glaucoma 1985; **7**: 54-62
3 Schoene RB, Abuan T, Ward RL, Beasley CH. Am J Ophthalmol 1984; **97**: 86-92
4 Van Buskirk EM. New Trends in Ophthalmol 1986; **104**: 1178-1184

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Prognostic significance of the pattern visual evoked potential in ocular hypertension

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Abstract

This paper reports a prospective study on 49 ocular hypertensive patients to evaluate the prognostic significance of transient abnormalities in the pattern visual evoked potential (VEP) in the development of glaucoma. Seven of 24 patients with VEP abnormalities at diagnosis of ocular hypertension developed glaucomatous field defects in the follow-up period as compared with none of 25 patients with normal VEPs at diagnosis. We conclude that appropriately designed pattern VEP testing is a valuable complement to careful (preferably computerised, static) perimetry. In addition, our findings support the contention that, in glaucomatous disease of the optic nerve, rudimentary pattern processing mechanisms – that is 'Y'-type units of the magnocellular pathways – may be affected earlier than luminance processing mechanisms.

The diagnosis of chronic simple glaucoma (CSG) in routine clinical practice is made when a raised intraocular pressure (IOP) of >21 mmHg is accompanied by characteristic optic nerve head cupping and visual field defects. Ocular hypertension (OH), however, presents us with more complicated problems in terms of both definition and management. In theory, OH is a benign elevation of IOP, that is, one that does not cause damage to retinal ganglion cells. In clinical practice, however, OH is defined as an elevation of IOP in the absence of detectable visual field loss. Clearly these two may not be the same, as they depend very much on the field technique used to ascertain early CSG. The difference between these definitions was demonstrated by Quigley and colleagues in pathological studies of optic nerves and retinae of OH and CSG sufferers. He showed that, by the time glaucomatous field loss was detected by Goldmann perimetry, up to 40% of optic nerve fibres were lost.¹ In a recent paper Quigley correlated retinal ganglion cell loss (demonstrated histologically) with visual field loss detected by the Octopus and Humphrey computerised static perimeters. He showed that a 20–40% reduction in ganglion cells corresponded to a loss of sensitivity of 5–10 dB.²

Although raised IOP is intimately associated with glaucoma, the two are not synonymous. Prospective studies of OH have suggested that less than 30–35% of patients will eventually develop CSG and it is impossible to predict which of them it will be.^{3–5} Consequently, clinical management is problematical. On the one hand benign ocular hypertensives could be subject to unnecessary and potentially hazardous treatment, while on the other, withholding treatment from those with incipient glaucoma could result

in accelerated field loss. Many clinicians, therefore, attempt a compromise and treat only those patients with an IOP of >30 mmHg in whom the probability of CSG is higher.

A number of alternative approaches have been advocated in an attempt to improve both detection and monitoring of OH and CSG. Stereoscopic optic disc⁶ and nerve fibre layer photography^{7,8} have been advocated as more sensitive indicators of damage as well as other tests of visual function, including colour vision,^{9,10} flicker perimetry,¹¹ contrast sensitivity,^{12,13} and recording of the visual evoked potential (VEP)^{14–17} and the pattern electroretinogram (PERG).^{18–24} The VEP to pattern stimulation has been shown to demonstrate not only attenuation in CSG, but delay of the P100 component of the so-called 'transient' VEP and phase shifting of the 'steady state' VEP.^{15,16} Interestingly, significantly delayed latencies have also been observed in 25–50% of OH eyes.^{16,17,25} Earlier work in this department demonstrated a poor sensitivity of the VEP to detection of CSG in patients with superior visual field defects due to the dominance of the inferior hemifield signal to the full field VEP response.²⁵ Consequently an alternative technique was devised in which VEPs to superior and inferior hemifields were elicited separately, and the overall illumination of the central and peripheral retina was more carefully controlled. In this large comparative study these modifications were found to improve the detection rate of CSG. In addition abnormalities were reported in nearly 50% of OH patients. It was suggested that such a large figure may partly be explained by the relatively poor sensitivity of the Goldmann perimeter in detecting early field defects, an observation confirmed by a number of comparative studies using computerised static perimetry.^{26,27}

The purpose of this study, therefore, was to examine the transient pattern VEP in a group of ocular hypertensive patients who were then followed up prospectively to see if the presence of VEP abnormalities was of any prognostic value in relation to the development of glaucoma.

Material and methods

SUBJECTS AND PATIENTS

Forty-nine patients diagnosed as having OH were selected from the glaucoma clinic at the Royal Victoria Infirmary between late 1984 and early 1989. All patients were subjected, at diagnosis, to full ophthalmological examination including Snellen visual acuity, applanation tonometry, gonioscopy, and funduscopy. Initial visual fields in 25 patients were recorded by the

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Goldmann perimeter (targets I4_e or I2_e) and in the other 24 by the Octopus 2000R automated perimetry (program 34).

A diagnosis of ocular hypertension was made when the following criteria were fulfilled: (1) 31 mmHg > IOP > 21 mmHg; (2) a healthy optic disc (cup/disc ratio < 0.6 with ophthalmoscopically normal neuroretinal rim and nerve fibre layer); (3) a full visual field.

Patients were excluded from the study if their visual acuity was < 6/9, either due to media opacity or concomitant choroidoretinal pathology. In addition patients with miotic pupils (either due to senile miosis or drugs) were excluded from the study, since miosis is known to influence the VEP.¹⁵

Repeat visual field and electrophysiological testing was performed in the latter part of 1989. All 49 patients had Octopus field testing, and in addition those initially diagnosed by kinetic perimetry were reassessed by this method. Average follow-up period was 3.2 years (0.9–5.8 yr). In addition 26 age matched, normal subjects were tested to establish VEP control ranges.

ELECTROPHYSIOLOGY

The checkerboard was produced by a video pattern generator (Medelec) on a high quality TV monitor (Barco).²⁸ Luminance (L) modulation of the pattern was selected to give the pattern reversal mode of stimulation of a rate of 2 reversals per second. Check subtense was selected to be 100', pattern contrast (defined as $L_{max} - L_{min} / (L_{max} + L_{min})$) set at 40% and patient-monitor distance adjusted so that the stimulus field subtended 33° × 26°. The monitor was surrounded by a light adapting screen which was adjusted to the same luminance as the space average luminance of the TV monitor, namely,

10.4 Cd.m⁻². The screen measured 1.9 m × 1.9 m and subtended 120° × 120° at the retina.

Silver/silver-chloride disc electrodes were attached to the scalp with collodion in the following positions as defined by Jasper²⁹: active-'O₂'; reference-'C₂'; earth-'P_z'. Electrode impedances were adjusted to be < 2 kohm in both active and reference leads. For inferior hemifield stimulation (IHS) a light emitting diode (LED) fixation spot was attached to the top centre of the monitor screen and for superior hemifield stimulation (SHS) it was attached to the bottom centre, thus ensuring appropriate positioning of the subject's fixation in relation to the stimulus. Depending upon the size of the response, either 64 or 128 epochs of 300 ms duration was amplified, averaged, and stored. Two averages were obtained to check for consistency, and quantitative analysis was performed on the average of the two. Monocular stimulation was performed throughout the study, the non-stimulated eye being occluded with a patch. Pupil diameter was measured at the conclusion of the test.

The latency of the P100 component was measured, as was peak-peak amplitude between the P100 and N150 peaks.

STATISTICAL TREATMENT OF RESULTS

In the establishment of control ranges for absolute values of VEP measures data from one eye were selected from each individual, at random, as data from both eyes do not constitute truly random variables.³⁰ The level of statistical significance throughout all experimentation was selected to be at the 1% level ($p < 0.01$). The effect of pathology was assumed to produce excursions from normality in one direction only – for example, latency increase, amplitude reduction – so that single-tailed Student's *t* test analysis was applied to all data.

Results

Representative VEPs from a control subject are shown in Fig 1, the responses to IHS being illustrated in the top half of the figure and those to SHS in the lower half. The characteristic P100 component and its succeeding component, the N150, are clearly evident in all responses. A striking feature of the data in relation to the two stimulating modes is the longer component latency to SHS as compared with IHS. This feature is associated with the differing characteristics of the retinocortical pathways subserving the inferior and superior hemiretinae.^{31,32} For the control group as a whole, normal ranges for

Control Subject (Age: 61)

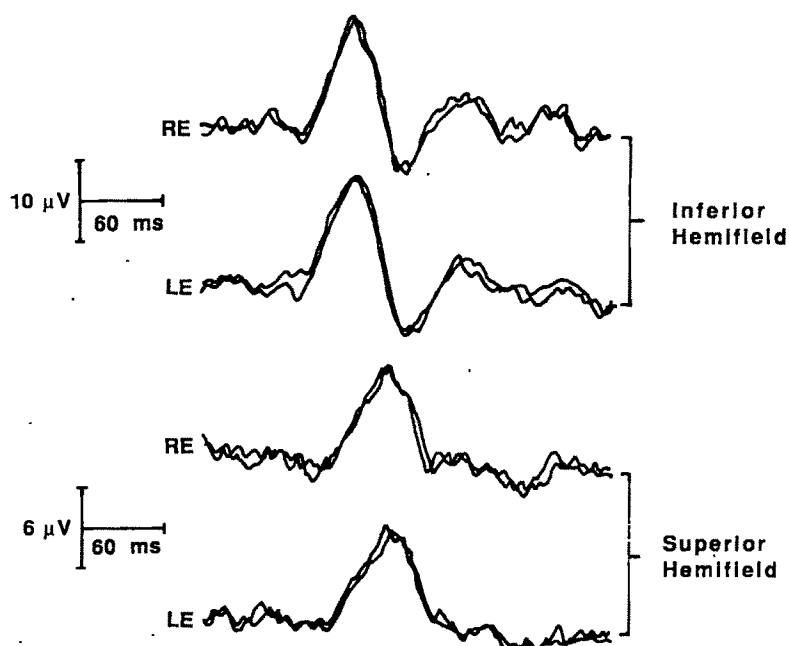


Figure 1 Pattern VEPs from a control subject. Upper traces to inferior hemifield stimulation, lower traces to superior hemifield stimulation.

Table 1 Normal ranges for VEP parameters

	Mean	SD	99% ci
(a) Absolute latency (ms):			
IHS (40-60 yr)	108.7	6.9	124.7
IHS (60-80 yr)	114.9	6.9	130.9
SHS	136.4	7.2	153.3
(b) Interocular latency differences (ms):			
IHS	1.6	1.1	4.0
SHS	2.4	2.2	7.0
(c) Interocular amplitude differences (μV):			
IHS	1.4	0.9	3.5
SHS	1.1	0.9	3.3

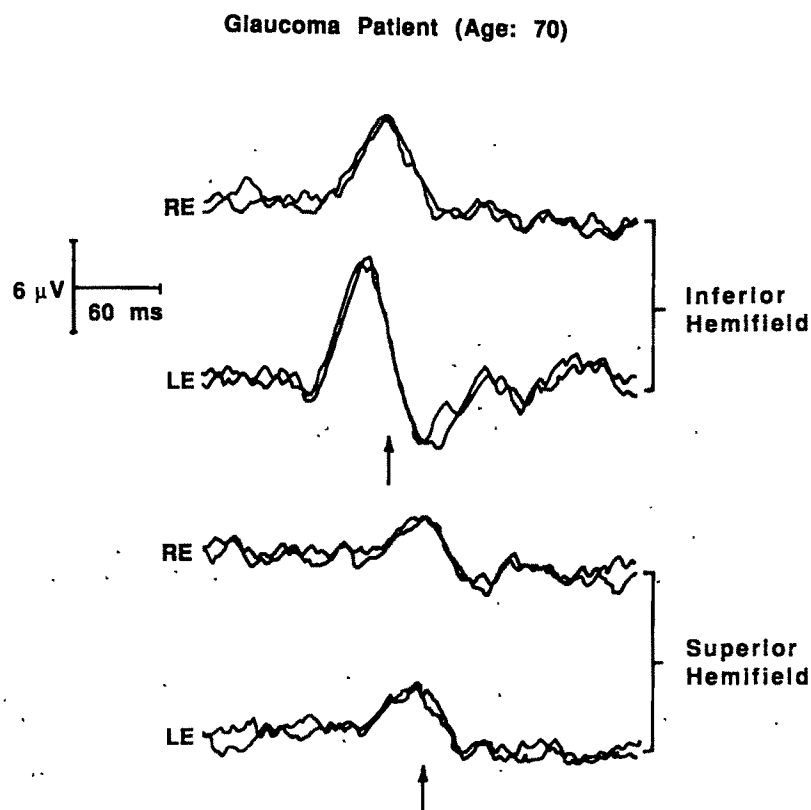


Figure 2 Pattern VEPs from an early CSG patient. Upper traces to inferior hemifield stimulation, lower traces to superior hemifield stimulation.

absolute P100 latency and interocular differences in both latency and amplitude were established (Table 1a-c). No sex differences were found, but there was a trend towards increasing latency with age for IHS. Consequently, absolute latency data were separated into two age bands. From these results 99% confidence limits (cl) were determined (Table 1). Absolute values of amplitude showed considerable interindividual variation, which resulted in a large standard deviation. Lower limits were therefore (nonsensically) below zero, thus precluding the clinical utility of this measure.

VEPs from a glaucoma patient are shown in Fig 2 (as an aid in comparing these data with those of normal persons, arrow markers indicate the upper 99% cl of the control ranges). It can be seen that to IHS there is a marked interocular difference in latency, the right eye responses having significantly longer latency than those from the left eye, even though *both* are within the normal range. There is also some attenuation of the former response as compared with the latter. The recordings to SHS do not show any differential effects but do have latencies towards the top end of the normal range. In relation to the patient group as a whole they, at initial presentation, showed latency abnormalities (absolute and/or interocular differences) in 16 of 49 patients (32.7%) (compared with two of 26 controls (7.7%)). All 16 had significant interocular differences in latency (nine had abnormalities to IHS and 11 had abnormalities to SHS) and two revealed an absolute latency delay. In relation to interocular amplitude abnormalities, 14 of the 49 (28.6%) were significant – again, this compared with two of 26 controls (7.7%). In addition, one patient had an unusual VEP waveform, and

Table 2 Diagnostic outcome at follow-up in relation to initial VEP

Initial VEP	OH	CSG	Reverted
Normal	23	0	2
Abnormal	16	7	1

Table 3 Comparison of initial and follow-up VEP for OH patients

Initial VEP	Follow up VEP	
	Normal	Abnormal
Normal	22	3
Abnormal	7	17

although detailed analysis of it was not feasible it was considered to be abnormal and was included in all subsequent analysis as such. Overall, 24 of 49 patients (49.0%) showed some sort of abnormality at initial diagnosis. Of these, 12 were initially assessed by Goldmann field and 12 by Octopus.

Reassessment of the OH group at follow-up resulted in a reassignment of diagnosis as shown in Table 2. The most significant feature of these data is that all seven who were subsequently confirmed as early CSG had an abnormal VEP on initial assessment. It should be noted that five of these were initially assessed by Goldmann perimetry and field defects were subsequently demonstrated by both this method and Octopus. The other two were assessed by the latter method alone. The additional 16 with abnormalities were, on reassessment, still regarded as OH. It is also interesting, and somewhat reassuring, to note that, of the 23 who had normal VEPs, none had developed signs of CSG by the end of the follow-up period. The 'reverted' column refers to those patients whose subsequent IOP readings were consistently found to be normal. A comparison between results of the follow-up VEPs and the initial recordings is shown in Table 3. The 17 patients who had consistently abnormal VEPs included the seven who developed glaucomatous damage. Of the seven whose results returned to normal four had an increase in latency in their fellow eye, resulting in a loss of the previously reported interocular difference. The remaining three had no such explanation for the return of their VEP to 'normality' and included the single patient from this group who 'reverted'. Of the 25 patients who initially had normal VEPs 22 remained normal, two developed interocular differences in latency, and one an interocular difference in amplitude. The VEPs

Table 4 Comparison of mean intertest changes in VEP latency

	Intertest mean	SD	Significance (df)*
(a) IHS			
OH (VEP normal)	-0.91	4.17	
OH (VEP abnormal)	+1.19	4.72	NS (37)
CSG	+4.33	7.74	p=0.015 (27)
(b) SHS			
OH (VEP normal)	-1.00	5.68	
OH (VEP abnormal)	+3.38	4.73	p=0.008 (37)
CSG	+6.83	8.77	p=0.006 (27)

* Degrees of freedom.

of the two patients who 'reverted' were normal on retesting.

We also compared the mean intertest changes in VEP parameters of those ocular hypertensives who initially had normal VEPs respectively with those who had abnormal VEPs but remained OH, and those who developed CSG (Table 4). In relation to the former some difference was demonstrated in latency, but this was significant for the SHS mode alone (Table 4b). As to the latter, notwithstanding the small number in the CSG group (seven), significance was observed for both stimulation modes, at the significance level shown (Table 4a, b). Mean intertest amplitude did not show any changes in either group.

Discussion

Though the earliest studies of the VEP in OH failed to reveal any abnormalities,^{14,15} in recent years there have been a number of reports showing changes.^{16,17,25} In addition there has been much enthusiasm concerning the potential application of the PERG in both ocular hypertension and early CSG,¹⁸⁻²⁴ where the main finding has been attenuation of the response. Consequently, its application in the diagnosis and management of these conditions has been advocated. However, it is well understood in visual electrophysiology that absolute amplitude is a 'soft' quantity, whereas latency, or more correctly in this particular context implicit time, is a 'hard' quantity, – that is, amplitude measurements demonstrate large interindividual variability, whereas latency/implicit time measurements show small interindividual variability. Therefore, as PERG implicit time has shown little or no change in glaucoma,²⁰ its clinical utility is vitiated by the significant overlap of amplitude distributions of control and OH/CSG populations.^{21,22} An attempt has been made to overcome this problem by adopting ratiometric techniques in relation to the measurement of PERG componentry,²⁴ and with some success. However, there are still problems, as measurement of amplitude has to be made with respect to a stable 'baseline', a condition notoriously difficult to achieve in the routine clinical setting.

With regard to the transient pattern VEP, Towle's group¹⁶ demonstrated significantly delayed latencies in 23% of OH patients, and subsequent studies using refined stimulation techniques have observed up to 47% of such patients with abnormalities.^{17,25} The incidence of 49% in this present study generally concurs with these previous findings. A recent study using the flash VEP²³ has attempted to advocate the use of this method clinically, but it has long been known in electrophysiological research that such potentials are limited by wide variability of amplitude within the normal population and large interindividual variation in form.²⁴ It is also impossible adequately to control retinal adaptation levels and exclude problems due to stray and scattered light. Consequently, the predictable finding of significant overlap in P1 amplitudes of control and pathological populations in glaucoma²³ does, we believe, preclude its use for this purpose.

To our knowledge this present report is the first published follow-up study undertaken to determine the prognostic significance of electrophysiological abnormalities in OH. The most striking feature of our results is that all seven patients who eventually developed glaucomatous field defects had VEP abnormalities at initial diagnosis of ocular hypertension. As a group they also showed increases in VEP latency at follow-up, thus demonstrating a deterioration of retinal ganglion cell function due to incipient glaucomatous damage. It must be conceded, however, that had the five who were initially classified by kinetic perimetry been subjected to more sensitive computerised static perimetry, their initial diagnosis might have been different. In relation to the 16 patients with VEP abnormalities at initial examination who have yet to develop field defects, we believe that they must be followed up carefully to determine whether they are in the early stages of glaucoma or whether they are false positives due to lack of specificity of the VEP. However, set against the latter possibility is the fact that, in common with the group who developed signs of glaucoma, they showed a significant increase in mean latency (albeit to SHS alone), strengthening the contention that they do indeed have incipient glaucoma. Thus we consider it is justifiable to assert that OH patients with VEP abnormalities at initial presentation are at higher risk of developing glaucoma.

With respect to the OH group with normal VEPs at diagnosis, none of them so far have developed field defects, and intertest comparisons have revealed marked stability of VEP parameters. Twenty-two of the original 25 patients in this group have maintained normality on repeat testing and therefore we consider can be regarded as at low risk of developing glaucoma. Three, however, have developed VEP abnormalities and obviously must be treated with more caution. There are problems of course, in giving the correct weight to measurements of interocular differences. These may be absent in symmetrical glaucoma, leading, falsely, to the reporting of normality. Intertest comparisons are of more value in this instance, as they may reveal deterioration of VEP parameters that one would fail to detect when comparing a single VEP with the normal range. This was illustrated in our study group, six of the 16 OH patients with VEP abnormalities at diagnosis were reported as having normal VEPs on follow-up. Intertest comparisons, however, revealed an increase in latency in the fellow eye of four of them, and therefore there is the distinct suspicion that they could be abnormal.

As no patient in the study had any concomitant neurophysiological or ophthalmological disorders, or confounding factors due to optical errors or media opacities which could have compromised the data, we are confident in ascribing the effects to early glaucomatous processes. The result of such damage is, we would argue, consistent with the theory that units with large receptive field size and high contrast sensitivity – the 'Y'-type cells of the magnocellular pathways – are damaged first in glaucoma.^{25,26} This is not an unreasonable

suggestion, as our VEP stimulation technique, namely, field size/location, check size/contrast, and surround illumination, generally matches the characteristics and retinal location of such units. We would thus argue that such factors are of considerable import in the design of VEP experimentation to maximise clinical effectiveness.

The transient pattern VEP is a straightforward investigation which takes 10–15 minutes in total to perform and requires the patient to fixate for only about 30–60 seconds at any one time. It thus requires less co-operation than conventional kinetic or computerised static perimetry and therefore has distinct advantages with regard to that group of patients who have difficulty in performing a field investigation. However, our current understanding of the effects of early glaucomatous pathology on visual function, coupled to the qualified conclusions of this modest follow-up study, do not allow us to advocate VEP methods as a substitute for careful static perimetry. What it does suggest is that the two techniques are complementary, the former giving us objective data on, primarily, *pattern* processing mechanisms, whereas the latter elicits subjective data on primarily *luminance* processing mechanisms. There is mounting evidence to support the contention that pattern mechanisms are affected in advance of luminance mechanisms in early glaucoma,³⁷ and the findings of this study are in concordance with these. Much work still needs to be done, however to expand our knowledge of such processes further. In addition more extended, prospective studies on larger patient cohorts are required before we can confidently support the pattern VEP as an earlier indicator of incipient glaucoma.

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- Quigley HA, Addicks EM, Green WR. Optic nerve damage in human glaucoma III. Quantitative correlation of nerve fiber loss and visual field defect in glaucoma, ischemic neuropathy, disc edema, and toxic neuropathy. *Arch Ophthalmol* 1982; 100: 135–46.
- Quigley HA, Dunkelberger GR, Green WR. Retinal ganglion cell atrophy correlated with automated perimetry in human eyes with glaucoma. *Am J Ophthalmol* 1989; 107: 453–64.
- Perkins ES. The Bedford glaucoma survey. I. Long-term follow-up of borderline cases. *Br J Ophthalmol* 1973; 57: 179–85.
- Kahn HA, Leibowitz HM, Ganley JP, et al. The Framingham Eye Study. I: Outline and major prevalence findings. *Am J Epidemiol* 1977; 106: 17–23.
- Aasved H, Hovding G. The Bergen Glaucoma Study: diagnostic criteria, epidemiology, prognostic factors and indicators for treatment. *Chibret International d'Ophthalmologie* 1987; 5: 4–19.
- Johnson CA, Keltner JL, Krohn MA, Portney GL. Photogrammetry of the optic disc in glaucoma and ocular hypertension with simultaneous stereo photography. *Invest Ophthalmol Vis Sci* 1979; 18: 1252–63.
- Airaksinen PJ, Nieminen H. Retinal nerve fiber layer photography in glaucoma. *Ophthalmology* 1985; 92: 877–9.
- Takamoto T, Schwarz B. Photogrammetric measurement of nerve fiber layer thickness. *Ophthalmology* 1989; 96: 1315–9.
- Fishman GA, Krill AE, Fishman M. Acquired color defects in patients with open angle glaucoma and ocular hypertension. *Mod Probl Ophthalmol* 1974; 13: 335–8.
- Gunduz K, Arden GB, Perry S, Weinstein GW, Hitchings RA. Colour vision defects in ocular hypertension and glaucoma. Quantification with a computer driven color television system. *Arch Ophthalmol* 1988; 106: 929–35.
- Campbell CJ, Rittler M. The diagnostic value of flicker perimetry in chronic simple glaucoma. *Ophthalmology* 1959; 63: 89–98.
- Arden GB, Jacobson JJ. A simple grating test of contrast sensitivity: preliminary results indicate value in screening for glaucoma. *Invest Ophthalmol Vis Sci* 1978; 17: 23–32.
- Hitchings RA, Powell DJ, Arden GB, Carter RM. Contrast sensitivity gratings in glaucoma family screening. *Br J Ophthalmol* 1981; 61: 107–13.
- Cappin JM, Nissim S. Visual evoked responses in the assessment of field defects in glaucoma. *Arch Ophthalmol* 1975; 93: 9–18.
- Sokol S, Domar A, Moskovitz A, Schwarz B. Pattern evoked potential latency and contrast sensitivity in glaucoma and ocular hypertension. *Doc Ophthalmol Proc Ser* 1981; 27: 79–86.
- Towle VL, Moskovitz A, Sokol S, Schwarz B. The visual evoked potential in glaucoma and ocular hypertension. Effects of check size, field size and stimulation rate. *Invest Ophthalmol Vis Sci* 1983; 24: 175–83.
- Howe JW, Mitchell KW. Visual evoked cortical potential to paracentral retinal stimulation in chronic glaucoma, ocular hypertension and an age-matched group of normals. *Doc Ophthalmol* 1985; 63: 37–44.
- Fiorentini A, Maffei L, Pirchio M, Porciatti V, Spinelli D. Pattern ERG in patients with unilateral alterations in ganglion cells. *Doc Ophthalmol Proc Ser* 1981; 31: 131–3.
- Wanger P, Persson HE. Pattern reversal electroretinograms in unilateral glaucoma. *Invest Ophthalmol Vis Sci* 1983; 24: 749–53.
- Howe JW, Mitchell KW. Simultaneous recording of pattern electroretinogram and visual evoked cortical potential in a group of patients with chronic glaucoma. *Doc Ophthalmol Proc Ser* 1984; 40: 101–8.
- Van Lith GHM, Ringens P, de Heer LJ. Pattern electroretinogram and glaucoma. *Dev Ophthalmol* 1984; 9: 133–9.
- Wanger P, Persson HE. Pattern reversal electroretinograms from normotensive, hypertensive, and glaucomatous eyes. *Ophthalmologica* 1987; 195: 205–8.
- Weinstein GW, Arden GB, Hitchings RA, Ryan S, Calthorpe CM, Odom JV. The pattern ERG in ocular hypertension and glaucoma. *Arch Ophthalmol* 1988; 106: 923–8.
- Odom JV, Feghali JG, Jin J, Weinstein GW. Visual function deficits in glaucoma: electroretinogram pattern and luminance nonlinearities. *Arch Ophthalmol* 1990; 108: 222–7.
- Mitchell KW. The visual evoked potential in the differential diagnosis of ocular hypertension and chronic simple glaucoma. Ph D thesis. University of Newcastle upon Tyne, 1987.
- Sommer A, Enger C, Witt K. Screening for glaucomatous visual field loss with automated threshold perimetry. *Am J Ophthalmol* 1987; 102: 681–4.
- Kriegstein GK, Screms W, Leydhecker W. Detectability of early glaucomatous field defects. A controlled comparison of Goldmann versus Octopus perimetry. *Doc Ophthalmol Proc Ser* 1980; 26: 19–24.
- Arden GB, Faulkner DJ, Mair C. A versatile television pattern generator for visual evoked potentials. In: Deamedt JE, ed. *Visual evoked potentials in man: new developments*. Oxford: Clarendon Press, 1977.
- Jasper HH. Report of the committee on methods of clinical examination in electroencephalography. *Electroencephalogr Clin Neurophysiol* 1958; 10: 370–5.
- Ederer F. Referencing clinical research papers for statistical content. (Editorial.) *Am J Ophthalmol* 1985; 100: 735–7.
- Lehmann D, Skrandies W. Multichannel evoked potential fields show different properties of human upper and lower hemiretina systems. *Exp Brain Res* 1979; 35: 151–9.
- Barber C, Galloway NR. Pattern evoked potentials as indicators of functional visual field asymmetries. *Doc Ophthalmol Proc Ser* 1981; 27: 229–37.
- Watts MT, Good PA, O'Neill EC. The flash stimulated VEP in the diagnosis of glaucoma. *Eye* 1989; 3: 732–7.
- Halliday AM. The visual evoked potential in healthy subjects. In: Halliday, AM, ed. *Evoked potentials in clinical testing*. London, Edinburgh: Churchill Livingstone, 1982: 71–120.
- Marx MS, Podos SM, Bodis-Wollner I, Lee PY, Wang RF, Severin C. Signs of early damage in glaucomatous monkey eyes: low spatial frequency losses in the pattern ERG and VEP. *Exp Eye Res* 1988; 46: 173–84.
- Quigley HA, Hendrickson A. Chronic experimental glaucoma in primates: blood flow study with iodantipyrine and pattern of selective ganglion cell loss. *Invest Ophthalmol Vis Sci* 1984; 25 (suppl): 225.
- Neima D, Le Blanc R, Regan D. Visual field defects in ocular hypertension and glaucoma. *Arch Ophthalmol* 1984; 102: 1042–5.

Ocular defects in infants of extremely low birth weight and low gestational age

Priscilla Burgess, Ann Johnson

Abstract

The eyes of 49 babies who weighed less than 1000 g at birth or who were born at or before 28 weeks gestation were examined at the age of 4 years. Twenty-one children were normal. The remaining 29 children (59%) had ocular abnormalities which ranged from mild amblyopia to blindness from retinopathy of prematurity. The need to examine children at risk is stressed.

The recent increase in survival of babies of extremely low birth weight (ELBW), that is, weighing less than 1000 g, and infants of low gestational age (28 weeks or less) has led to increasing concern about their long term outcome. Overall less than half of these babies survive,¹ though survival rates as high as 63%² are achieved in some areas. A recent meta-analysis of a large number of follow-up studies of ELBW infants has shown that just over a third of all survivors (36%) were impaired.³ Most of this impairment is of neurological origin – that is, cerebral palsy, sensory deficit, and learning difficulties. The most serious ocular defect in these babies is retinopathy of prematurity (ROP), and several studies have confirmed that the risk of ROP is inversely related to birth weight.⁴⁻⁶ In particular, cicatricial, binding ROP is more common in infants weighing under 1 kg at birth.^{5,7-9}

The literature contains little information on the outcome of babies of low birth weight and low gestational age from the ophthalmological as distinct from a developmental standpoint. Saigal *et al*¹⁰ described the findings at the age of 2 years of a group of ELBW infants from a geographically defined region in Canada. She noted an overall incidence of ROP of 38%. There were eight children with one or both eyes blind from ROP from a population of 110 survivors (7%). Two children had reduced vision due to optic atrophy (2%), 17 were myopic (16%), 13 had strabismus (12%), and one had nystagmus (1%). Keith and Kitchen¹¹ in a similar study noted ocular lesions in 33% of survivors: 10% had cicatricial ROP, 3% had optic atrophy, 17% had considerable refractive error, and 19% had squint. Hungerford *et al*¹² in a study of babies born before 33 weeks of gestation found ocular pathology in 15%. The commonest problem was refractive error; 8% had ROP, and 5% had delayed visual maturation. Both these studies were hospital based and described survivors from one centre.

In 1984 a study was undertaken of all infants born to mothers resident in the Oxford Region and who weighed less than 1000 g at birth or who were born at or before 28 weeks' gestation. The

eyes of 72% of this cohort of ELBW babies were also examined. The main purpose of this report is to give a detailed description of the ocular findings.

Patients and methods

Sixty-eight of 127 (54%) babies born alive to mothers in the Oxford Region and who weighed less than 1000 g or who were born at or before 28 weeks' gestation survived to their fourth birthday. The eyes of 49 of the 68 survivors were examined during a two-year period from June 1987 to June 1989. The mean age of the children (25 girls, 24 boys) at the time of visual assessment was 4 years 4 months (range 3 years 8 months to 4 years 11 months).

The ocular assessment consisted of the following: The parents were questioned about eye disease either in the child or in the family, with particular reference to strabismus and myopia. A detailed neonatal history was available from the hospital notes. The ocular motility was assessed, and examination included pursuit and saccadic eye movements, and a cover test for near and distance. Visual acuity was measured where possible with a linear Snellen chart or linear Sheridan Gardner or Kay pictures. In non-verbal children the ability to fix and follow small targets was assessed. We also undertook confrontation visual field tests using finger counting in the quadrants; TNO tests (named after authors – Toegepast, Natuurwetenschappelijk, Onderzoek to measure stereopsis; Slit-lamp examination; and refraction and indirect ophthalmoscopy following the instillation of cyclopentolate 1%.

Not all children were examined by an ophthalmologist as neonates. Whether or not such an examination was performed depended on the intensive care unit in which the child was treated.

Results

The ocular findings in 21 to 49 (43%) children were normal. The remaining 28 children (59%) were found to have a variety of ocular abnormalities (Table 1).

RETINOPATHY OF PREMATURITY

Two of 49 (4%) children had severe cicatricial

Table 1 Ocular defects

	Number of children	Percentage of children
Retinopathy of prematurity	2	4
Strabismus	12	25
Myopia	5	10
Optic nerve head abnormalities	5	10

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ROP. The first was born at 26 weeks' gestation and weighed 720 g. She suffered from respiratory distress syndrome, was ventilated until the fifth day of life, and had supplemental oxygen in a headbox until the sixteenth day. She also had a patent ductus arteriosus which was treated with indomethacin. At 6 months of chronological age she was noted to have roving eye movements and was found to have bilateral closed funnel retinal detachments. At age 4 years she was blind in both eyes and entirely retarded, with a severe communication disorder.

The second child with severe cicatricial ROP was born at 24 weeks' gestation and weighed 632 g. She was ventilated for six weeks and sustained an intraventricular haemorrhage. When assessed the right eye was normal, but the left was divergent and had an eccentric macula with a dragged disc and temporal vasculature. Interestingly this eye was highly hypermetropic and astigmatic. This child had made good developmental progress, and neither child with ROP had associated cerebral palsy.

Another child when seen during the neonatal period had acute ROP (grade 2 maximally) but was normal when seen at age 4. A further child had mild mid peripheral retinal pigmentary speckling as her only abnormality at age 4.

STRABISMUS

Twelve of 49 (24%) children had strabismus (Table 2). Of the eight convergent cases, six were non-accommodative, one partially accommodative, and one infantile. There were four divergent squints, three constant and one intermittent.

Three children were myopic (range -2 to -8 dioptres). All three had a non-accommodative pattern esotropia.

Nine of the 12 squinting children had reduced acuity in one or both eyes. In six this was due to sensory deprivation, in three it was associated with myopia, one had hypoplastic discs, one had optic atrophy and one had ROP. Six of the children had neurological or behavioural problems. Four had cerebral palsy, one was developmentally delayed, and the sixth was hyperactive.

A further child not included above had a past history of strabismus but was not squinting when seen at 4 years. She also had no evidence of stereopsis.

Table 2 Associations found with strabismus

	Convergent non accommodative	Convergent partially accommodative	Convergent infantile	Divergent
Number	6	1	1	4
Myopia	3			
Amblyopia	5	1		3
Neurological defect	5			1

Table 3 Optic nerve head abnormalities

	Number of children	Bilateral	Unilateral	Neurological deficit
Optic atrophy	2	1	1	2
Optic nerve hypoplasia	1	1		1
Optic disc drusen	1		1	
Tilted discs	1	1		

OPTIC NERVE HEAD ABNORMALITIES

Five of 49 (10%) children had either unilateral or bilateral abnormalities of the optic nerve head (Table 3). There were two children with optic atrophy. The first had unilateral involvement and a visual acuity of 6/18 in the affected eye. The second with bilateral involvement was also cortically blind and could not fix or follow a target with either eye. Of the remaining three children one had bilateral optic nerve hypoplasia and very poor acuity in both eyes, another had a large irregularly shaped left optic disc probably due to buried drusen and a visual acuity of 6/12 in the affected eye. The third had bilateral tilted discs with mild oblique astigmatism but normal visual acuity in both eyes.

CORTICAL BLINDNESS

One child was 'cortically blind'. Born at 26 weeks she had had a particularly difficult neonatal period. Following an intraventricular haemorrhage she developed hydrocephalus, which was treated by a ventriculo-peritoneal shunt. Subsequently she developed at least two episodes of meningitis and blockage of the shunt. When examined she had severe spastic quadriplegia, entire developmental delay, mild myopia and bilateral optic atrophy. It was extremely difficult to quantify the degree of visual impairment attributable to optic nerve disease and that related to the postchiasmal pathways.

Five children had mild to moderate impairment of visual acuity in one or both eyes unassociated with any abnormality of the media fundus or error of refraction and may have had minor cortical visual impairment.

MYOPIA

Five of 49 (10%) children were myopic (range -1.50 to -8.00 D) (Figure 1). In only one was the vision correctable to 6/6 in each eye. Three had reduced vision due to anisometropia and squint and one had both optic atrophy and cortical blindness. Two children had family history of myopia in close relatives. A family history in two other children was unavailable because they had been adopted. Three of the five myopic children were found to have straightening of the temporal vascular arcades but no other stigmata of ROP. They had not been ventilated for longer than 24 hours and all weighed over 900 g.

Discussion

This study has been largely concerned with the detection of anatomical and functional defects of the visual system in a group of ELBW babies delivered to residents of a geographically defined area. The high incidence of ocular morbidity of 59% could have been due to bias in the sample, because children with known or obvious defects were more likely to be available for ophthalmic examination. The group of children not seen did not differ from those who were seen in mean birth weight or mean gestational age (Table 4). Neither did the proportion of children with an

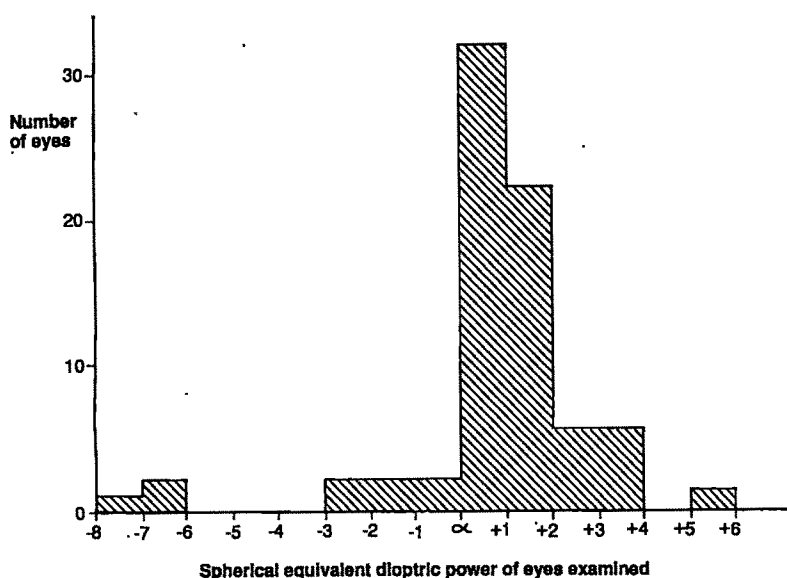


Figure 1 Refractive data.

impairment differ in the two groups. All 19 infants not seen were screened by health visitors; seven of 19 were referred to specialist eye services. None of these referred children were found to have an ophthalmic abnormality. If we assume that, although other systems were impaired, all 19 children were ophthalmologically normal, the incidence of ocular defect in this population is 43% (29/68).

RETINOPATHY OF PREMATURITY

The two children with cicatricial ROP had several of the recognised risk factors for this condition, namely extreme prematurity, extremely low birth weight, severe respiratory distress syndrome, and intraventricular haemorrhage. Several studies from the United States have shown that the incidence of blindness from ROP in infants with birth weights of less than 1.5 kg ranges from 1.8% to 4%,^{5,9} but the distribution is markedly skewed towards those weighing less than 1 kg. Cicatricial disease occurs in 22–42% of these smallest survivors,^{2,9} whereas 5–11% of them are blind. Ng *et al*¹³ in a geographically defined study in Britain confirmed the greater severity of ROP with shorter gestation and lower birth weight. The early and frequent examinations of babies in their study identified a very high incidence of acute ROP. The incidence of cicatricial disease was low, and they suggest that this may be partly due to racial factors. The incidence of cicatricial disease in our study may be underestimated owing to the difficulties of examining the peripheral fundus of children of this age. Indeed three of the myopic children had straightening of the temporal vascular arcades and probably had ROP. If these children are included, the incidence of cicatricial ROP was 5/49 or 10%.

STRABISMUS

The incidence of strabismus is higher in preterm than full term babies. Kushner,¹⁴ for example, found an incidence of 34% in a group of babies with regressed ROP, 16% in a group of preterm

Table 4 Birth weight, gestational age, and impairment code of all survivors to 4 years

	Children seen	Children not seen
Number	49	19
Male	25 (51%)	7 (37%)
Birthweight (g), mean (SD)	1009 (201)	1068 (251)
Gestational age (weeks), mean (SD)	27.9 (1.9)	27.6 (1.2)
Number of children with impairment coded 3 or 4*	27 (55%)	8† (67%)

* Impairment code 3=impairment in one or more areas resulting in mild to moderate disability. Impairment code 4 includes cerebral palsy, severe sensory loss, total developmental delay.
† Impairment codes not available for seven infants (unavailable for assessment because overseas, etc.)

babies without ROP, and 5% in a comparable group of full term babies. Anisometropia inducing strabismus and amblyopia only partly explains these findings. The incidence of strabismus in this study (24%) is higher than in similar studies, where incidences of 12% and 19% have been noted. One explanation for this is the older population seen in the Oxford study, with an increased risk of accommodative esotropia and consecutive divergence.

In this study one-third of the squints were divergent, a much higher proportion than that seen elsewhere in similar but not strictly comparable groups and again may be due to the age of the population examined. In Black's study¹⁵ of visual disorders associated with cerebral palsy he also noted a convergence:divergence ratio of 2.3:1.

The strong association between myopia and convergent squint has also been noted by Keith and Kitchen¹¹ and Kushner¹³; the mechanism is presumably a type of sensory deprivation esotropia. The incidence of squint is higher in children with neurological deficit, especially cerebral palsy.¹⁵ The mechanism for this is not fully explained, but children with the spastic type of cerebral palsy are the most likely to have ocular defects. In them the pathology is extensive and diffuse, with periventricular and subcortical haemorrhage and cortical atrophy.

OPTIC NERVE ABNORMALITIES

The association between cerebral palsy and ocular morbidity is well recognised.^{16,17} The 4% incidence of optic atrophy in this study compares with reported incidences of 2%¹⁰ and 3%.¹¹ Possible mechanisms for optic atrophy are that it is secondary to hydrocephalus and also is associated with cerebral palsy.¹⁵ In the same study hypoplastic discs were seen in 3/120 (2.5%) children with severe spastic cerebral palsy; our child with hypoplastic discs also had severe spastic cerebral palsy. There were two cases of relatively innocuous disc abnormalities (one tilted disc and buried drusen) which have not previously been recorded as a feature of low birth weight.

CORTICAL BLINDNESS

Diffuse cortical deficit may be associated with visual impairment without any abnormality of the eyes or anterior visual pathways.¹⁸ The acuity in these children is usually limited to counting

fingers or less. Colour vision and the ability to perceive movement is better than form perception. There is a broad spectrum of disability in this condition. It has recently become apparent that visual acuity in children who were born prematurely is less good than in full term controls. This seems to be the result of some other factor associated with prematurity.^{19,20} It may be that the five children in our study with decreased acuity without any ophthalmic explanation have the latter type of cortical visual impairment.

MYOPIA

There is a well recognised relationship between myopia and ROP.²¹⁻²⁴ Myopia has been described as a feature of all grades of ROP but occurring in up to 80% of patients with cicatricial disease.²⁵ Asymmetrical myopia can result in severe anisometropic amblyopia in an eye with only minimal cicatricial changes. Several studies have reported that the myopia is not solely due to increased axial length but may have lenticular and corneal components.²⁶⁻²⁸

Because of the high incidence of ocular morbidity in ELBW babies it is recommended that such children should not only be examined by an ophthalmologist in the nursery to detect ROP but also followed up during early childhood to detect, and if possible treat, any associated ocular disorder. Some of these children have multiple handicaps, and visual defects may be overlooked, with serious visual and educational implications. Babies of extremely low birth weight contribute minimally to the total ocular pathology seen in early childhood. However, the risk of abnormality is high, and they warrant thorough ophthalmic assessment and care.

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- 1 Saigal S, Rosenbaum P, Hattersley B, Milner R. Decreased disability rate among three year old survivors weighing 500-1000 g at birth. *J Pediatr* 1989; 114: 839-46.
- 2 Cooke RWI. Referral to a regional centre improves outcome in

- extremely low birthweight infants. *Arch Dis Child* 1987; 62: 619-21.
- 3 Aylward GP, Pfeiffer SI, Wright A, Verhulst SJ. Outcome studies of low birth weight infants published in the last decade: A meta-analysis. *J Pediatr* 1989; 115: 515-20.
- 4 Patz A. Retrolental fibroplasia. *Surv Ophthalmol* 1969; 14: 1-29.
- 5 Gunn TR, Easdown J, Outerbridge EW, Aranda JV. Risk factors in retrolental fibroplasia. *Pediatrics* 1980; 65: 1096-100.
- 6 Hammer ME, Mullen PW, Ferguson JG, et al. Logistic analysis of risk factors in acute retinopathy of prematurity. *Am J Ophthalmol* 1986; 102: 1-6.
- 7 Bauer CR. The occurrence of retrolental fibroplasia in infants of birth weight 1000 grams and less. *Clin Res* 1978; 26: 824A.
- 8 McCormick AQ. Retinopathy of prematurity. *Curr Probl Pediatr* 1977; 7: 11.
- 9 Shahinian L, Malachowski N. Retrolental fibroplasia. A new analysis of risk factors based on recent cases. *Arch Ophthalmol* 1978; 96: 70-4.
- 10 Saigal S, Rosenbaum P, Stoskopf B, Sinclair JC. Outcome in infants 501 to 1000 gm birth weight delivered to residents of the McMaster Health Region. *J Pediatr* 1984; 105: 969-76.
- 11 Keith CG, Kitchen WH. Ocular morbidity in infants of very low birth weight. *Br J Ophthalmol* 1983; 67: 302-5.
- 12 Hungerford J, Stewart A, Hope P. Ocular sequelae of preterm birth and their relation to ultrasound evidence of cerebral damage. *Br J Ophthalmol* 1986; 70: 463-8.
- 13 Ng YK, Fielder AR, Shaw DE, Levene MI. Epidemiology of retinopathy of prematurity. *Lancet* 1988; ii: 1235-8.
- 14 Kushner BJ. Strabismus and amblyopia associated with regressed retinopathy of prematurity. *Arch Ophthalmol* 1982; 100: 256-61.
- 15 Black P. Visual disorders associated with cerebral palsy. *Br J Ophthalmol* 1982; 66: 46-52.
- 16 Breakey AS. Ocular findings in cerebral palsy. *Arch Ophthalmol* 1955; 53: 852-6.
- 17 Smith VH. Strabismus in cerebral palsy. *Br Orthopt J* 1965; 22: 84-94.
- 18 Jan JE, Groeneweld M, Sykanda AM, Hoyt CS. Behavioural characteristics of children with permanent cortical visual impairment. *Dev Med Child Neurol* 1987; 29: 571-6.
- 19 Fiedelius HC. Ophthalmic changes from age of 10 to 18 years. A longitudinal study of sequels to low birth weight. II. Visual acuity. *Acta Ophthalmol (Kbh)* 1981; 59: 64-70.
- 20 Sebris SL, Dobson V, Hartman EE. Assessment and prediction of visual acuity in 3 to 4-year-old children born prior to term. *Hum Neurobiol* 1984; 3: 87-92.
- 21 King MJ. Retrolental fibroplasia: a clinical study of two hundred and thirty-eight cases. *Arch Ophthalmol* 1950; 43: 694-711.
- 22 Reese AB, Stepanik J. Cicatricial stage of retrolental fibroplasia. *Am J Ophthalmol* 1954; 38: 308-16.
- 23 Birge HL. Myopia caused by prematurity. *Trans Am Ophthalmol Soc* 1955; 53: 219-30.
- 24 Fletcher MC, Brandon S. Myopia of prematurity. *Am J Ophthalmol* 1955; 40: 474-81.
- 25 Tasman W. Late complications of retrolental fibroplasia. *Ophthalmology* 1979; 86: 1724-40.
- 26 Majima A. Studies on retinopathy of prematurity II. Fundus appearance and ocular functions in cicatricial phase of very low birthweight babies. *Jpn J Ophthalmol* 1977; 21: 421-35.
- 27 Hibino Y, Takahashi M, Majima A. Studies on ocular functions of cicatricial retinopathy of prematurity. Measurement of refractive elements. *Jpn J Clin Ophthalmol* 1978; 32: 655-62.
- 28 Gordon RA, Donzis PB. Myopia associated with retinopathy of prematurity. *Ophthalmology* 1986; 93: 1593-8.

Multifocal IOL implantation: 16 cases

Ilse Vanderschueren, Thierry Zeyen, Benjamin D'heer

Abstract

We interpreted the clinical data from 16 eyes with a 3M multifocal implant and compared them with data from 16 monofocal implants with the same follow-up period. The multifocal implant has several disadvantages: a lower initial visual acuity, a higher frequency of posterior synechiae, and slightly more difficult ophthalmoscopy than with conventional lenses. The great advantage of the multifocal implant is the good near visual acuity without additional correction.

The 3M multifocal IOL was implanted in 16 eyes of 12 patients; four patients received a bilateral 3M multifocal IOL implant. The patients ranged in age from 39 to 86 years (mean 73 years). The length of follow-up ranged from three to 16 weeks (mean seven weeks).

All the patients in our study group underwent an extracapsular cataract extraction with IOL implantation according to the envelope technique, except for one patient who had a secondary IOL implantation (in the sulcus ciliaris) after a previous extracapsular lens extraction for a traumatic cataract.

The 3M multifocal IOL is an entirely polymethyl methacrylate (PMMA) lens. It creates near and far vision through the use of precision diffractive optics rather than relying on conventional refractive optics alone.¹

This bifocal vision is realised by the design of the 3M IOL, which consists of a diffractive microstructure superimposed on the posterior surface of a conventional lens. This micro-

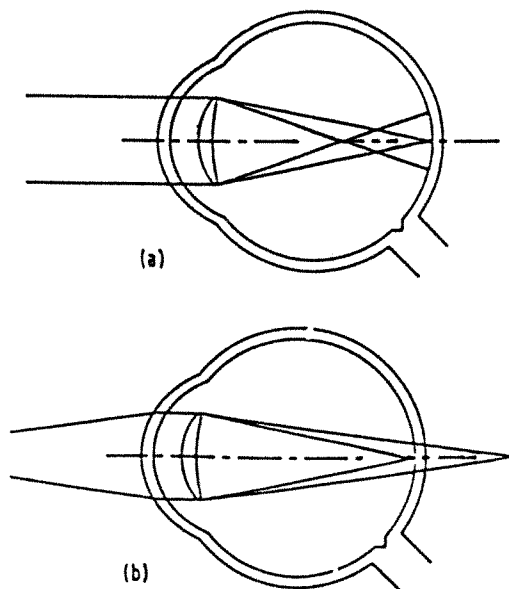


Figure 2 'Simultaneous vision' imaging with an IOL which has two powers: (a) distant vision; (b) near vision.

structure is composed of a series of concentric sloped rings which diffract light in a specific way to create two foci (Fig 1).

The base power of the lens (distance focus) is equivalent to that of a conventional lens of the same dioptric power (Fig 2). The 'add-' power (near focus) is provided by the correct diffractive microstructure on the posterior surface.

Results

For each case we studied several parameters and compared the results with those from 16 monofocal lenses implanted on the same day by the same surgeon and thus with exactly the same postoperative follow-up. These parameters included refraction, visual acuity, glare testing, slit-lamp examination, and near vision.

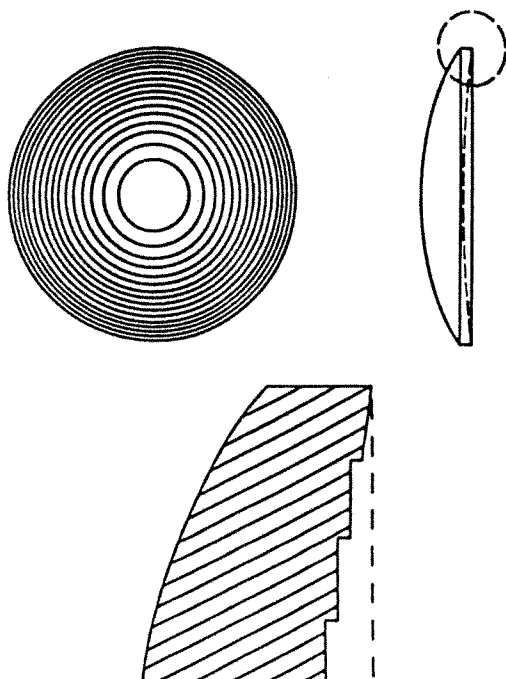


Figure 1 The 3M diffractive bifocal lens.

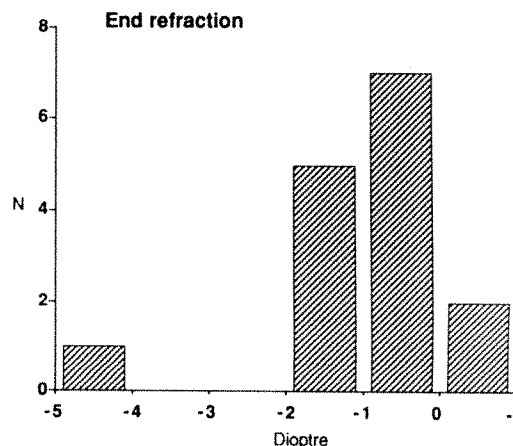


Figure 3 Postoperative refraction in spherical equivalents of the multifocal cases.

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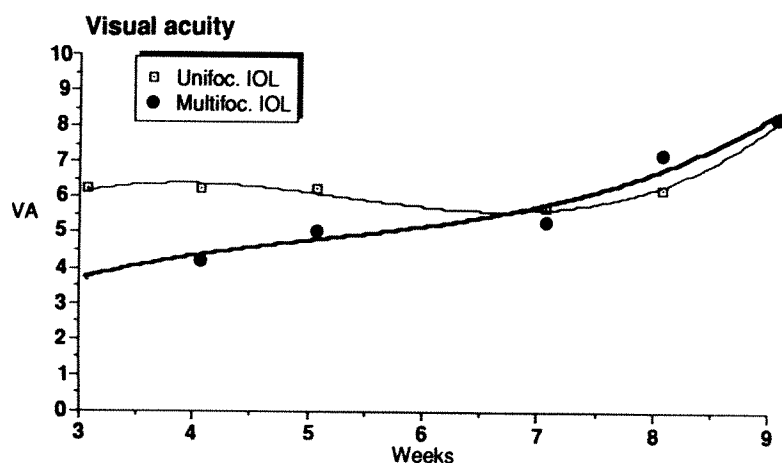


Figure 4 Evolution of the postoperative visual acuity.

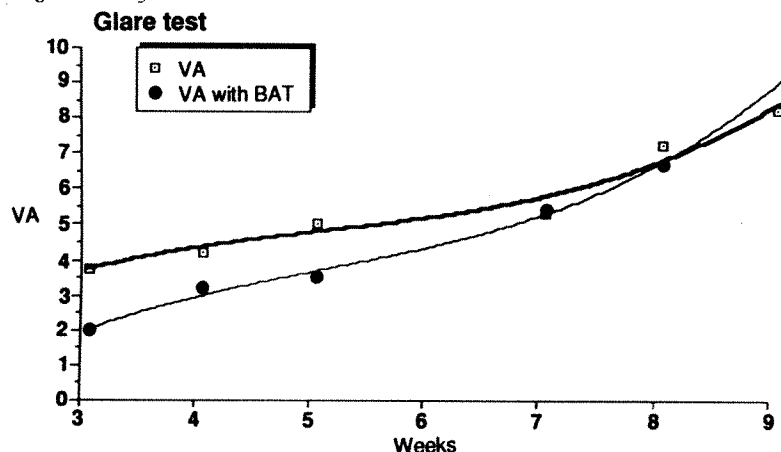
The 'final' postoperative refraction noted in spherical equivalents was in the slightly myopic range for most of the cases. The histogram on Figure 3 represents the refraction distribution of the multifocal cases. It was exactly superposable on the monofocal distribution with the exception of one isolated case of high myopia, which was unexpected and not planned. A slight postoperative myopia is an acceptable result when using monofocal lenses; with multifocal lenses, however, the goal is emmetropia.

When comparing the evolution of the postoperative visual acuity between the two groups (Fig 4), we found that during the first weeks this visual acuity was a little lower for the multifocal cases. But after a period of seven weeks one can see the two curves joining each other. At that time the visual acuity was almost similar for both groups. This phenomenon is not of major importance on a long term basis, though it induces a lower degree of initial postoperative satisfaction.

We also studied the glare phenomenon (Fig 5), but only for the multifocal lenses. With the 'Brightness acuity tester' there was a slight decrease in visual acuity during the first postoperative weeks. But from the eighth week on we found that glare was no longer a problem. One patient, however, continued to mention glare spontaneously in the longer term.

By slit-lamp examination a surprisingly high frequency of posterior synechiae was found. This phenomenon is probably due to the configuration of this type of lens, especially to its higher anterior convexity. The anterior capsule

Figure 5 Influence of glare on the visual acuity for the multifocal cases. BAT = brightness acuity tester.



NEAR VISION

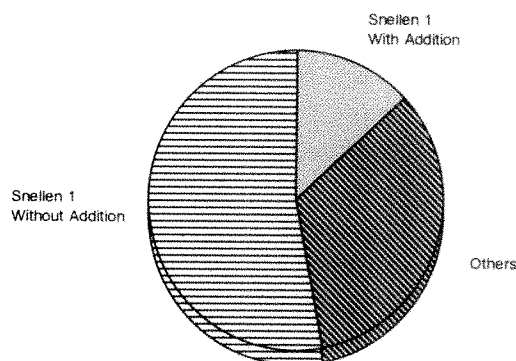


Figure 6 Efficiency of the near focus of the multifocal IOL.

is compressed between the iris and lens, which favours the formation of synechiae. The postoperative amount of flare and number of cells in the anterior chamber was comparable in both groups after four weeks of follow-up.

A longer follow-up period is certainly necessary to evaluate whether the irregular surface of this lens induces inflammatory reactions in the longer term.

The main advantage of this lens is undoubtedly the near vision (Fig 6). Most of the patients ('Snellen 1 without addition') could read the smallest text of the Snellen chart, and this by using their correction for far vision. The second group of patients ('Others') could not read the smallest text, probably owing to a slight cystoid macular oedema. To verify if these patients will ultimately succeed in reading Snellen 1 a longer follow-up period is necessary.

The third group of patients ('Snellen 1 with addition') could read the smallest text, but only with additional correction for near vision. These patients have probably not yet succeeded in finding the use of their near focus. Patients with a multifocal IOL presumably need an adaptation period, which might last a few months, before they discover the optimal use of their two foci.²

As an illustration of the use of these two foci, Figure 7 shows two automatic perimetries of the same patient with a multifocal IOL and an emmetropic postoperative refraction. The perimetry shown in Figure 7A was performed without a corrective glass. The patient used his focus for near vision. During the perimetry shown in Figure 7B a corrective glass of 2.5 dioptres was used; here the patient used his focus for far vision. The deficits can be perfectly superposed. This example indicates that this patient could switch, unconsciously and with great ease, from the use of far focus to near focus – and with a comparable visual result.

Discussion

We compared 16 eyes which underwent a multifocal IOL implantation with 16 eyes with a monofocal implant. Several parameters were studied. The average postoperative refraction was in the slightly myopic range in both groups. This was less desirable for the multifocal implants, where the aim is emmetropia. Lens calculation methods will have to be refined to obtain a higher number of emmetropic cases.³

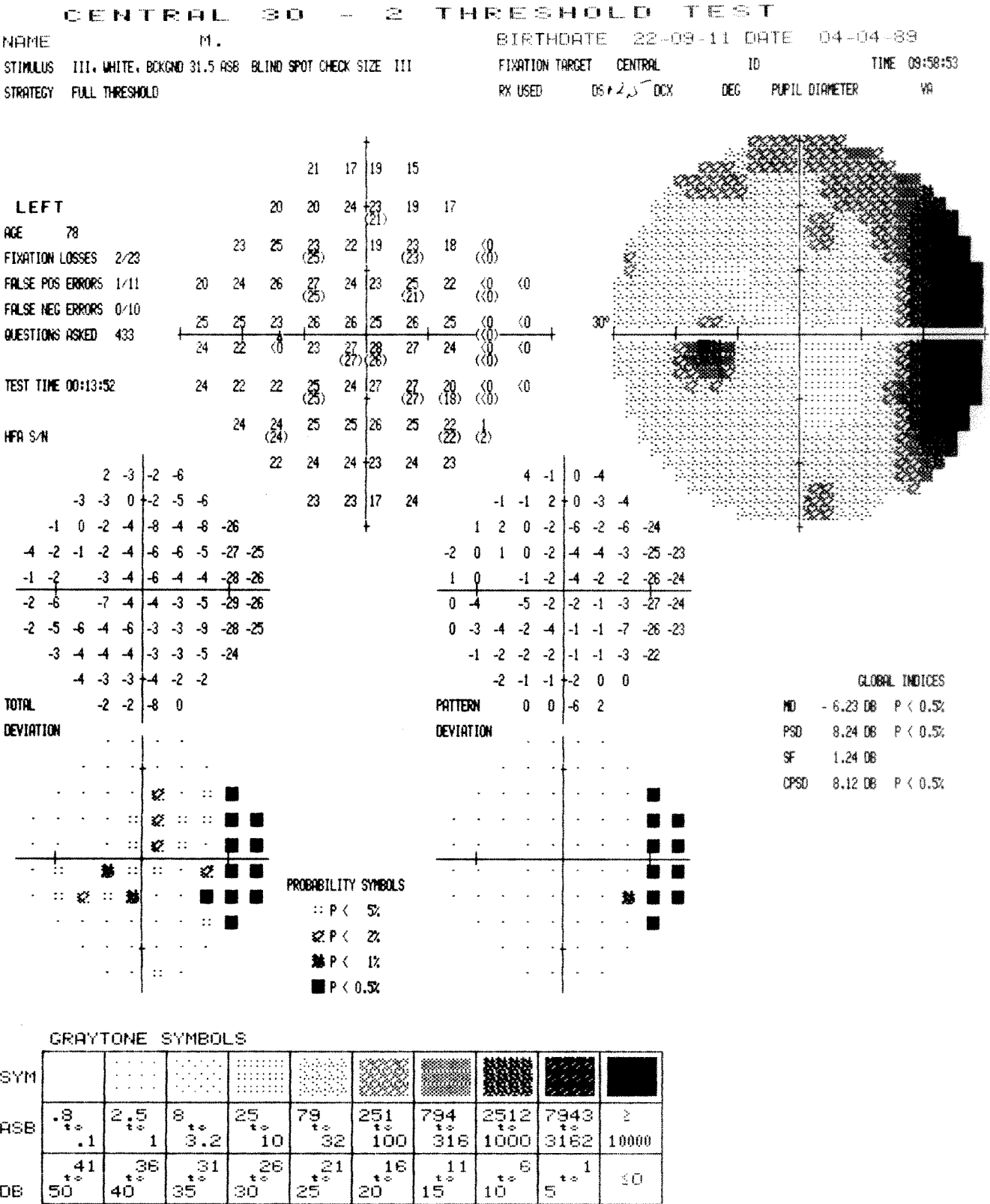


Figure 7B

older, inactive patients.⁴ The fact that this advantage might influence the indication for IOL implantation (implanting an IOL at the presbyopic age with almost no cataract or none at all) will probably be a matter for debate in future. A parameter we did not study is the contrast sensitivity. The study of Olsen and Corydon⁵ indicates that there is a decrease in contrast sensitivity for near vision, not for distance vision,

making the near focus somewhat less efficient than the far focus.

1 Simpson MJ. The diffractive multifocal intraocular lens. *Eur J Implant Refract Surg* 1989; 1: 115-21.
2 Percival P. Early experience with the diffractive bifocal lens. *Eur J Implant Refract Surg* 1989; 1: 3-4.
3 Donald T. Multifocal IOLs will challenge surgical skills. *Ocular Surgery News* 1989; 7(15): 1, 18-9.
4 Pow Chong G. Multifocal IOLs in Asia. *Ocular Surgery News* (international edition) 1990; 1(5): 1, 7-8.
5 Olsen T, Corydon L. Contrast sensitivity in patients with a new type of multifocal intraocular lens. *J Cataract Refract Surg* 1990; 16: 42-6.

Effect of anaesthesia on intraocular blood flow

Rosemary Robinson, Mary White, Patrick McCann, John Magner, Peter Eustace

Abstract

Pulsatile ocular blood flow, intraocular pressure, systemic blood pressure, and heart rate was measured in two groups of 15 patients. One received lignocaine 1.5 mg/kg intravenously prior to induction. There was a significant increase in intraocular pressure after suxamethonium, which was not associated with any rise in ocular blood flow. Both the IOP and ocular blood flow increased significantly after tracheal intubation. A rise in ocular blood flow reflects the stress response associated with intubation. Lignocaine failed to attenuate either response.

Laryngoscopy and endotracheal intubation can cause an increase in both intracranial and intraocular pressure (IOP).^{1,2} Suxamethonium has also been associated with an increase in IOP.³ The mechanism by which this is brought about is uncertain. Murphy *et al*⁴ showed that the major increase in IOP occurs immediately after endotracheal intubation rather than after the intravenous administration of suxamethonium. As a direct continuation of this study we examined the effect of administration of suxamethonium and endotracheal intubation on ocular blood flow to study the cause of these findings.

Intraocular pressure and pulsatile ocular blood flow (OBF) were measured by the Langham OBF System.⁵ Briefly, this instrument is based on the principle that blood flow to the eye is pulsatile. With each heart beat a bolus of blood is pumped into the eye which alters the intraocular pressure. From previously calculated pressure volume curves the change in pressure can be converted to a known volume. When multiplied by the heart rate per minute, the pulsatile flow to the eye per minute can be calculated. The IOP is measured with a sensitive electronic pneumatonometer which can record IOP at 30 ms intervals, giving a total of 30 pressure readings during each IOP pulsation. Thus our accurate and reproducible recording of systolic and diastolic IOP is recorded and the change in IOP can be easily measured.

Materials and methods

Thirty patients giving informed consent and undergoing general anaesthesia, requiring intubation, for elective surgery were studied pro-

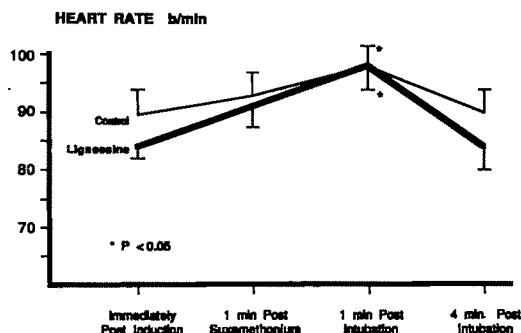


Figure 1 There is a significant increase one minute after intubation. b/min=beats per minute.

pectively. All patients were American Society of Anesthesiologists groups 1/II.⁶ Patients with a history of glaucoma, cataract, hypertension, diabetes, or carotid artery disease were excluded from the study. They were grouped by random number allocation into two groups of 15 on a double blind basis. Group 1 received intravenous lignocaine 1.5 mg/kg pretreatment one minute before induction, while group 2 received a placebo of 10 ml of saline.

All received diazepam 10 mg orally one hour prior to surgery. All were induced with a sleep dose of thiopentone 4-5 mg/kg, followed by suxamethonium 1.5 mg/kg one minute later, followed by endotracheal intubation one minute later. They were then maintained on a mixture of oxygen and nitrous oxide and enflurane.

The IOP and OBF were measured by the Langham OBF System, and the heart rate and mean blood pressure were measured simultaneously with a Dynamap. Measurements were taken immediately after induction at loss of the eyelash reflex, one minute after suxamethonium just prior to laryngoscopy, one minute after tracheal intubation, and four minutes later. The results were analysed by Student's *t* test for continuous variables.

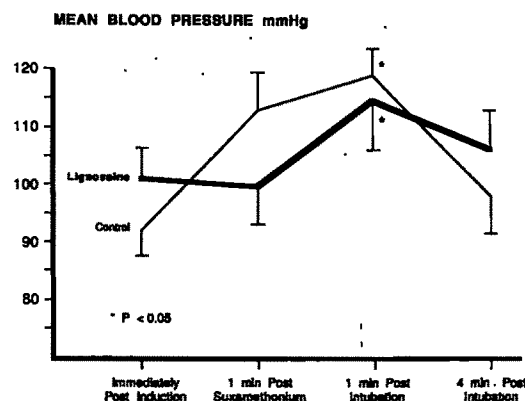


Figure 2 There is a significant increase one minute after intubation. There is no significant difference between the two groups at any stage.

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Table 1 Data for patient subgroups: mean (SD)

	Placebo	Lignocaine
Age	47.36 (16.19)	52.33 (16.99)
Sex M:F	7:8	9:6
Weight	71.36 (9.22)	67.24 (8.42)

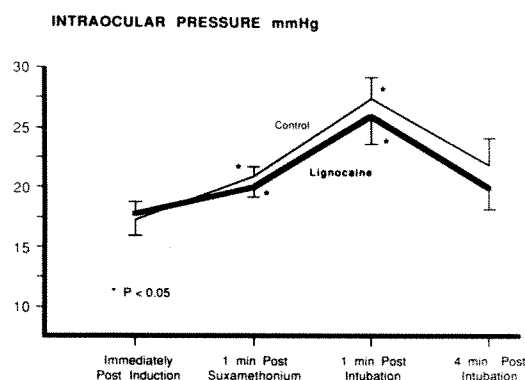


Figure 3 There is a significant increase one minute after suxamethonium and a further significant increase one minute after intubation.

Results

Both groups were evenly matched for age, sex, and weight (Table 1). There was no significant difference in heart rate and mean blood pressure between group 1 and group 2 at any time (Figs 1, 2). Both parameters showed a significant increase from baseline one minute after endotracheal intubation ($p < 0.05$).

The ocular haemodynamics are shown in Figures 3 and 4. There was a significant decrease in OBF in the control group immediately after suxamethonium ($p < 0.05$). Flow in the lignocaine group, however, remained at postinduction levels. There was a significant increase in IOP ($p < 0.05$) in both groups at this time. After intubation there was an even greater rise in IOP associated with a significant increase in OBF ($p < 0.05$) in both groups. All 4 parameters returned to baseline 4 minutes after intubation.

Discussion

Poulton and James⁷ demonstrated that the cough reflex in awake subjects is suppressed by lignocaine 1.5 mg/kg. Donegan and Bedford¹ also showed that lignocaine reduced the increase in intracranial pressure associated with tracheal suction in comatose patients. Drenger and Pe'er² reduced the increase in IOP after tracheal intubation by intravenous lignocaine. Murphy *et al.*⁴ however, have shown that lignocaine 1.5 mg/kg does not prevent the rise in IOP seen after administration of suxamethonium and tracheal intubation. Our results agree with this study, as lignocaine did not appear to alter any of the parameters measured in either group.

It is uncertain how suxamethonium increases IOP. Some workers believe it is due to sustained contraction of the extraocular muscles.⁸ Hess and Pilar⁹ demonstrated two types of muscle fibres in the extraocular muscle of the cat. The Felderstruktur respond with a slow tonic contraction when exposed to acetylcholine or depolarising relaxants. The Fibrillenstruktur, in

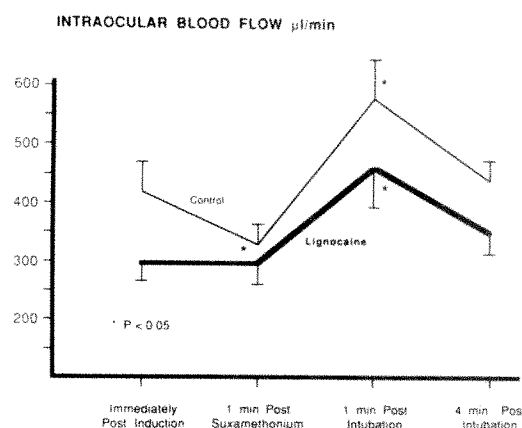


Figure 4 There is a significant decrease in the control group one minute after suxamethonium. Both groups show a significant increase one minute after intubation.

contrast, respond with a twitch response. The former predominate, and it is proposed that sustained contraction puts increased tension on the globe and thereby increases IOP. However, administration of D-tubocurarine, which should counteract the depolarising action of suxamethonium, does not alter its effect on IOP.¹⁰ Adams and Barnett¹¹ have proposed that the increase in IOP is due to choroidal vasodilatation. Our study shows no increase in ocular blood flow after intravenous administration of suxamethonium. Therefore the controversy persists.

After intubation there is an increase in heart rate and blood pressure. This reflects the stress response associated with tracheal intubation. As the eye is an essential organ, this is associated with increased blood flow to this area and thus an increase in IOP.

In conclusion, the major increase in intraocular pressure occurs owing to increased blood flow to the eye as part of the stress response of endotracheal intubation.

- 1 Donegan MF, Bedford RF. Intravenously administered lidocaine prevents intracranial hypertension during endotracheal suctioning. *Anesthesiology* 1980; 52: 516-8.
- 2 Drenger B, Pe'er J. Attenuation of ocular and systemic responses to tracheal intubation by intravenous lignocaine. *Br J Ophthalmol* 1987; 71: 546-8.
- 3 Cook JH. The effect of suxamethonium on intraocular pressure. *Anaesthesia* 1981; 70: 359-65.
- 4 Murphy DF, Eustace P, Unwin A, Magner JB. Intravenous lignocaine pretreatment to prevent IOP rise following suxamethonium and tracheal intubation. *Br J Ophthalmol* 1986; 70: 596-8.
- 5 Langham ME, Farrell R, O'Brien V, Silver D, Schilder P. Blood flow in the human eye. *Acta Ophthalmol (Kbh)* 1989; 67 (suppl 191): 9-13.
- 6 American Society of Anesthesiologists. New classification of physical status. *Anesthesiology* 1963; 24: 111.
- 7 Poulton TJ, James FM. Cough suppression by lidocaine. *Anesthesiology* 1979; 50: 470-2.
- 8 Lincoff HA. The effect of succinylcholine on intraocular pressure. *Am J Ophthalmol* 1955; 40: 501-10.
- 9 Hess A, Pilar G. Slow fibres in the extraocular muscles of the cat. *J Physiol (Lond)* 1963; 169: 780-98.
- 10 Meyers EF, Krupin T, Johnson M, Zink H. Failure of nondepolarizing neuromuscular blockers to inhibit succinylcholine induced increased intraocular pressure: a controlled study. *Anesthesiology* 1978; 48: 149-51.
- 11 Adams AK, Barnett KC. Anaesthesia and intraocular pressure. *Anaesthesia* 1966; 21: 202-10.

Herpes simplex keratitis in renal transplant patients

Israel Kremer, Aaron Wagner, Dan Shmuel, Alexander Yussim, Zaki Shapira

Abstract

Five out of 430 patients (1.16%) undergoing kidney transplantation developed an atypical clinical picture of herpetic dendritic keratitis within four weeks after surgery. It was manifested by multiple dendrites, located mainly in the corneal periphery or the limbus, developing in relatively uninflamed eyes. The response to acyclovir therapy was prolonged and took at least three weeks. Additionally, subepithelial infiltrates with ultimate scarring developed in all patients. Disciform keratopathy was not found. This clinical course is ascribed to the patients' immunosuppressed state.

Patients and methods

The records of all patients undergoing kidney transplantation in the Department of Organ Transplantation, Beilinson Medical Center, between the years 1980 and 1989 were reviewed independently by two of the authors. The charts of those patients affected with active herpetic dendritic keratitis were studied and the following parameters were evaluated: (a) timing of infection following transplantation; (b) previous herpetic infections; (c) clinical course of corneal herpetic disease; (d) extraocular manifestations of herpetic infection; (e) response to therapy; and (f) immunosuppressive therapy.

The relatively high incidence of extraocular herpes simplex virus (HSV) infection as well as infections by other members of the herpes virus group in immunosuppressed patients has been reported in several studies.¹⁻¹² These HSV infections result from the reactivation of latent HSV infection rather than from primary HSV infection from an exogenous source.^{3,8} The reported rate of extraocular HSV reactivation for renal transplant patients varies widely. For example, Schooley *et al*¹⁰ detected HSV infection in 18% of their patients, while Korsager *et al*⁹ isolated this virus from 54% and Pass *et al*⁸ from 66% of allograft recipients. These variable results probably depend on the category of patients studied, the frequency with which HSV isolation was attempted, different study protocols, and the fact that the immunosuppressive therapy of these patients is not alike.¹⁻¹² In addition Greenberg *et al*¹¹ reported a difference between the rate of HSV isolation (46.8%) and the formation of manifest HSV lesions (31.8%), meaning that not all kidney transplant patients in whom the virus is isolated will develop the typical herpetic lesions.

In contrast to the numerous studies reported on extraocular HSV infections in renal transplant patients we found scarce information in the English literature¹³ on the clinical course and rate of HSV keratitis in these patients. Therefore the purpose of the current retrospective study was to evaluate the prevalence of dendritic herpetic keratitis and its clinical appearance in kidney transplanted patients being treated with immunosuppressive therapy.

Results

Four hundred and thirty patients underwent kidney transplantation between the years 1980 to 1989. Five of these patients (1.16%) developed acute dendritic keratitis between 10 days and four weeks after surgery. Their ages ranged from 36 to 42 years (Table 1). All the patients were treated immediately following transplantation by triple therapy, which included prednisone 2 mg/kg, azathioprine 2.5-3.0 mg/kg, and cyclosporin-A 3-5 mg/kg. During the first month after surgery the steroid treatment was

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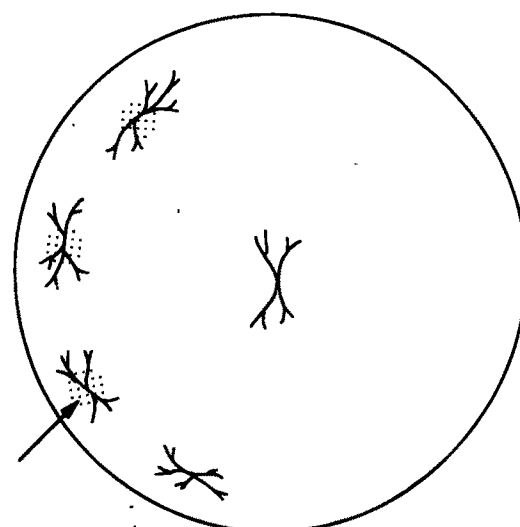


Figure 1 Schematic drawing of active dendritic keratitis in patient no. 3. Note the stromal infiltrates (arrow) and the peripheral location of most of the dendrites.

Table 1 Patients' data

Patient	Age	Timing post-transplantation	No. of dendrites	Location		Duration	Sub-epithelial infiltrates	Ciliary injections	Conjunctival injection	Eyelid skin lesions
				Central	Peripheral					
1	40	2 weeks	4	1	3	3 weeks	Present	Absent	Minimal	Present
2	42	10 days	6	2	4	3 weeks	Absent	Absent	Absent	Present
3	36	4 weeks	5	1	4	4 weeks	Present	Absent	Absent	Absent
4	39	3 weeks	4	1	3	4 weeks	Absent	Absent	Minimal	Present
5	41	2 weeks	4	-	4	4 weeks	Present	Absent	Absent	Absent

tapered to 20 mg per day, while the dosage of the other two medications was not changed. Subsequently the cyclosporin dosage was monitored so that a concentration of 140–200 ng/ml whole blood was achieved. The immunological profile and natural killer activity were not examined routinely in the patients included in the study. It should also be stressed that the patients did not receive preventive systemic acyclovir treatment. None of these patients could recall any previous corneal or eyelid herpetic infection. Three patients out of five had an associated herpetic skin eruption in the lower eyelid on the same side as the affected eye, which appeared several days before the corneal infection. In all five patients the herpetic infection was found to be unilateral, and there were multiple dendrites, most of them located either in the corneal periphery near the limbus (Fig 1) or at the limbus itself. There was no associated ciliary injection, and conjunctival hyperaemia was minimal or absent. Viral cultures taken from the epithelial lesions and the immunofluorescence tests revealed the presence of HSV.

The clinical course of the epithelial disease seemed to be prolonged in all the patients despite treatment with acyclovir ointment five times daily. This treatment had to be continued for three to four weeks until normal looking epithelium was observed. In all patients the course was protracted by small subepithelial nummular infiltrations under some of the epithelial dendrites, leading to superficial scarring, without any associated signs of uveitis. The classical picture of disciform keratitis did not develop during a follow-up period of four to six years, and no recurrence was noted in any patient.

Discussion

Viral infections still represent an important cause of complications and failure in the early post-transplantation period as a consequence of heavy initial immunosuppression.^{9–12} Natural killer (NK) cells play an important part in most defence mechanisms against viral infections.¹⁴ Cauda *et al*¹⁵ have presented data which suggest that the impairment of NK cells and T-cell activity is responsible for the increased risk of viral infections in transplant recipients receiving chronic immunosuppression.

The HSV, like the other members of the herpes virus group, has a longstanding close adaptation to its host.¹⁶ This virus has the capacity to establish latent, persistent infection in neural ganglia and probably also the lacrimal gland.¹⁶ From these sources it is periodically reactivated, causing viral shedding and transmission to new susceptible hosts and is thus found ubiquitously even in isolated populations.¹⁷ In addition, Tullo *et al*¹⁸ presented data on the isolation of HSV from corneal discs of patients with chronic stromal keratitis.

As much as 80% of the healthy human population is estimated to be infected by HSV-1, but only a small percentage of these manifest herpetic disease.^{19,20} As this virus has been isolated from the saliva and tears of asymptomatic individuals,¹⁶ symbiosis appears to be the most common relationship between humans and

HSV-1. Both virus and host immune factors may contribute to the maintenance of herpes virus infections at a subclinical level.

We expected, therefore, that herpetic epithelial corneal disease would be more frequent in immunosuppressed patients who have had a kidney transplant in comparison with the normal general population, serving as a control group for our study. According to several large epidemiological studies the incidence of dendritic keratitis is difficult to estimate, as many cases are subclinical infections and others are undiagnosed.^{19–23} It ranges between 59 and 500 new cases per million per year in Denmark^{19,21} and 1 to 1.6 per million per year in Tunis.²³

With regard to the results of our retrospective study, about one out of 100 renal transplant patients developed dendritic keratitis, which seems to be a higher rate of infection than the expected rate in the normal population.^{19–23} However, it is lower than the rate of systemic HSV infection or isolation in allograft patients, which ranges widely from 18%¹⁰ to 66%.⁹

The clinical course of herpetic corneal disease found in our patients was similar to herpetic keratitis developing in healthy patients following long-term local steroid treatment. These patients also show multiple dendrites, the majority of them located in the corneal periphery.

In three out of the five presented patients the virus probably penetrated into the superficial stroma, causing subepithelial keratitis and nummular superficial stromal scarring, though disciform keratopathy did not develop. In addition the antiviral treatment had to be continued for at least three weeks in order to eliminate the active viral infection. The fact that none of the patients developed disciform keratopathy is supported by the evidence provided by Metcalf and Kaufman.²⁴ They showed that congenitally athymic nude mice failed to develop stromal lesions following corneal infection with HSV-1, while their euthymic litter mates did develop disciform-like stromal lesions.

Russel *et al*²⁵ extended these findings by showing that nude mice could be made susceptible to stromal lesions following adoptive transfer of T lymphocytes from HSV-1 infected euthymic mice.

The atypical clinical picture of HSV keratitis found in our patients is similar to that reported by Howcroft and Breslin¹³ in renal transplant recipients. First, they also found multiple dendrites in the peripheral cornea, adjacent to the limbus; secondly, the keratitis was associated with minimal circumcorneal injection or none at all; and, thirdly, all their patients had presumed herpes virus infections of the skin. The differences are that we did not find evidence for bilateral disease or signs of uveitis, which were both reported by these authors¹³ in 50% of their patients. Moreover, the clinical course of herpetic disease was more prolonged in our patients and necessitated a longer period of antiviral treatment. The postoperative treatment regimen was also somewhat different, as our patients received a combination of steroids, cyclosporin-A, and azathioprine, while Howcroft and Breslin's patients received steroids and azathioprine only.¹³ Unfortunately these authors¹³ did

not present data on the rate of HSV corneal infection among their patients.

To conclude, HSV corneal disease is a relatively frequent postoperative complication in renal transplant immunosuppressed patients, though less frequent than the overall rate of systemic viral infections in these patients. Furthermore, our patients showed that the clinical course of this corneal infection is atypical and that it is coupled with minimal conjunctival reaction. Therefore one should be aware of this complication in this specific group of patients, mainly during the early postoperative period, when high doses of immunosuppressive medications are given and the NK cell activity of the patients is suppressed.²⁶ Ophthalmic consultation should be provided as soon as any mild ocular symptoms develop, though the patient's eyes may look uninfamed.

- 1 Pien FD, Smith TF, Anderson CF, Webel ML, Taswell HF. Herpes virus in renal transplant patients. *Transplantation* 1978; 16: 489-95.
- 2 Rifkind D. Cytomegalovirus infection after renal transplantation. *Arch Intern Med* 1965; 116: 554-8.
- 3 Naragi S, Jackson GG, Jonasson O, Yamashiroya M. Prospective study of prevalence, incidence and source of herpes virus infections in patients with renal allografts. *J Infect Dis* 1977; 136: 531-40.
- 4 Armstrong JA, Evans AS, Ras N, Ho M. Viral infections in renal transplant recipients. *Infect Immun* 1976; 14: 970-5.
- 5 Naraqi S, Jonasson O, Jackson GG, Yamashiroya HM. Clinical manifestations of infections with herpes viruses after kidney transplantation. *Ann Surg* 1979; 188: 234-9.
- 6 Takahashi K, Yagisawa T, Teraoka S, et al. Viral infections in kidney transplant patients immunosuppressed with cyclosporine. *Transplant Proc* 1987; 19: 2142-9.
- 7 Greger B, Doller G, Schareck WD, Muller GH, Mellert J, Hopt UT, Bockhorn H. Incidence and clinical course of CMV (and herpes simplex) infections under triple drug therapy. *Transplant Proc* 1987; 19: 4057-60.
- 8 Korsager B, Spencer ES, Mordhorst CH, Andersen HK. Herpes virus hominis infections in renal transplant recipients. *Scand J Infect Dis* 1975; 7: 11-9.
- 9 Pass RF, Whitley RJ, Whelchel JD, Diethelm AG, Reynolds DW, Alford CA. Identification of patients with increased risk of infection with herpes simplex virus after renal transplantation. *J Infect Dis* 1979; 140: 487-92.
- 10 Schooley RT, Hirsch MS, Colvin RB, et al. Association of herpes virus infections with T-lymphocyte-subset alterations, glomerulopathy and opportunistic infections after renal transplantation. *N Engl J Med* 1983; 308: 307-13.
- 11 Greenberg MS, Friedman H, Cohen SG, Oh SH, Laster L, Starr S. A comparative study of herpes simplex infections in renal transplant and leukemic patients. *J Infect Dis* 1987; 156: 280-7.
- 12 Whitley RJ, Levin M, Barton N, et al. Infections caused by herpes simplex virus in the immunocompromised host. Natural history and topical acyclovir therapy. *J Infect Dis* 1984; 150: 323-9.
- 13 Howcroft MJ, Breslin CW. Herpes simplex keratitis in renal transplant recipients. *Can Med Assoc J* 1981; 124: 292-4.
- 14 Rager-Zisman B, Allison AC. Mechanism of immunologic resistance to herpes simplex virus I (HSV-1) infection. *J Immunol* 1976; 116: 35-40.
- 15 Cauda R, Citterio F, Tamburrini E, et al. Natural killer activity against viral targets in cyclosporine-treated renal allograft recipients. *Transplant Proc* 1988; 20 (suppl 2): 186-9.
- 16 Kaufman HF, Brown DC, Ellison EC. Herpes virus in the lacrimal gland, conjunctiva and cornea of man - a chronic infection. *Am J Ophthalmol* 1968; 65: 32-5.
- 17 Darougar S, Wishart MS, Viswalingam ND. Epidemiological and clinical features of primary herpes simplex virus ocular infection. *Br J Ophthalmol* 1985; 69: 2-6.
- 18 Tullo AB, Easty DL, Shimeld C, Stirling PE, Darville JM. Isolation of herpes simplex virus from corneal discs of patients with chronic stromal keratitis. *Trans Ophthalmol Soc UK* 1985; 104: 159-75.
- 19 Norn MS. Dendritic (herpetic) keratitis: 1. Incidence - seasonal variations - recurrence rate - visual impairment - therapy. *Acta Ophthalmol (Kbh)* 1970; 48: 91-107.
- 20 Leopold IH, Serry TW. Epidemiology of herpes simplex keratitis. *Invest Ophthalmol Vis Sci* 1963; 2: 298-303.
- 21 Mortensen KK, Sjolic AK. Keratitis dendritica - an epidemiological investigation. *Acta Ophthalmol (Kbh)* 1979; 57: 750-3.
- 22 Pavan-Longston D. Ocular viral diseases. In: Galasso GJ, Mertigan TC, Buchanan RA, eds. *Antiviral agents and viral diseases of man*. New York: Raven Press, 1990: 323-60.
- 23 Whitcher JP, Dawson CR, Hoshiwara I, et al. Herpes simplex keratitis in a developing country - natural history and treatment of epithelial ulcers in a developing country. *Arch Ophthalmol* 1976; 94: 587-92.
- 24 Metcalf JF, Kaufman HE. Herpetic stromal keratitis: evidence for cell-mediated immunopathogenesis. *Am J Ophthalmol* 1976; 82: 827-34.
- 25 Russell RG, Nasais MP, Larsen HS, Rouse BT. Role of T-lymphocytes in the pathogenesis of herpetic stromal keratitis. *Invest Ophthalmol Vis Sci* 1984; 25: 938-44.
- 26 Smilie AE, Petrie JJB, Rigby RT. Effect of immunosuppression regimen and in vitro lymphokines on natural killer activity in renal transplantation. *Clin Transplant* 1989; 3: 273-8.

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NEWS ITEMS

BOOK REVIEWS

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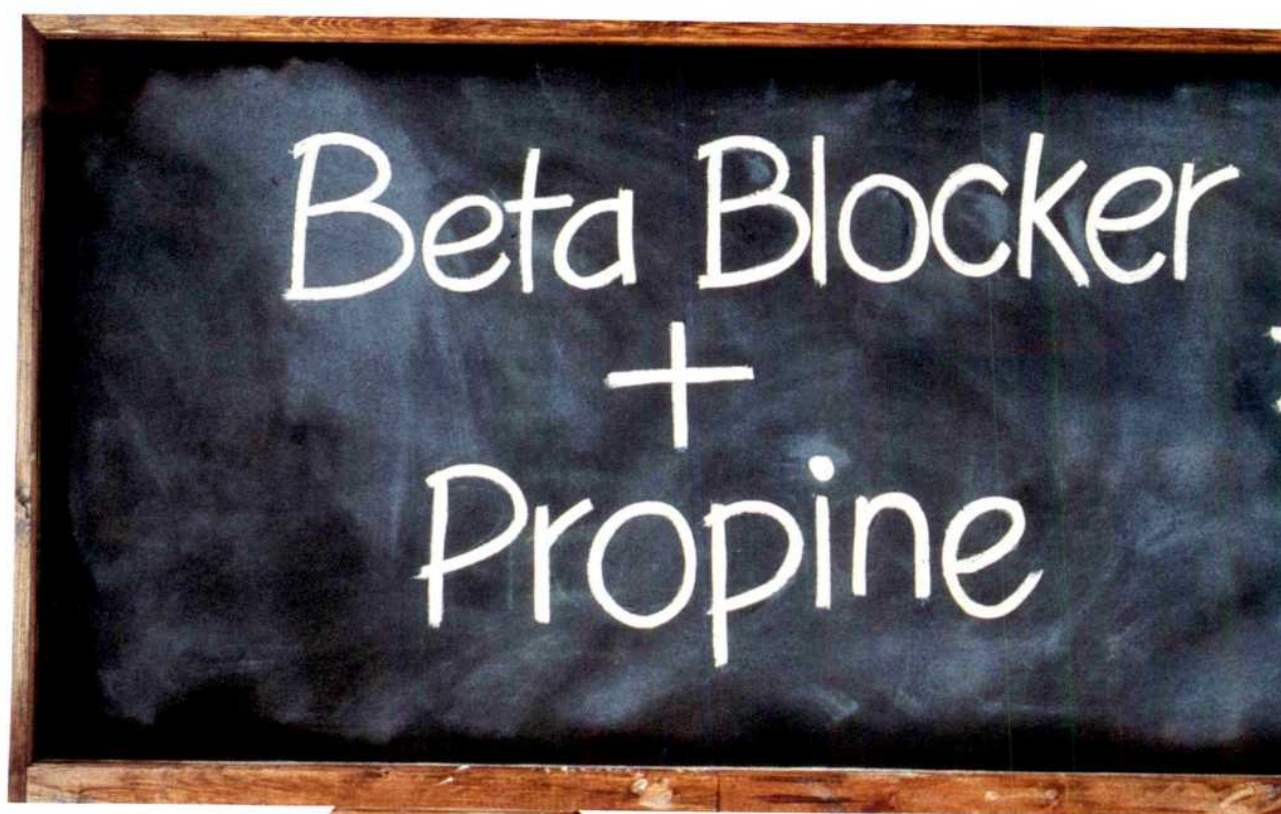
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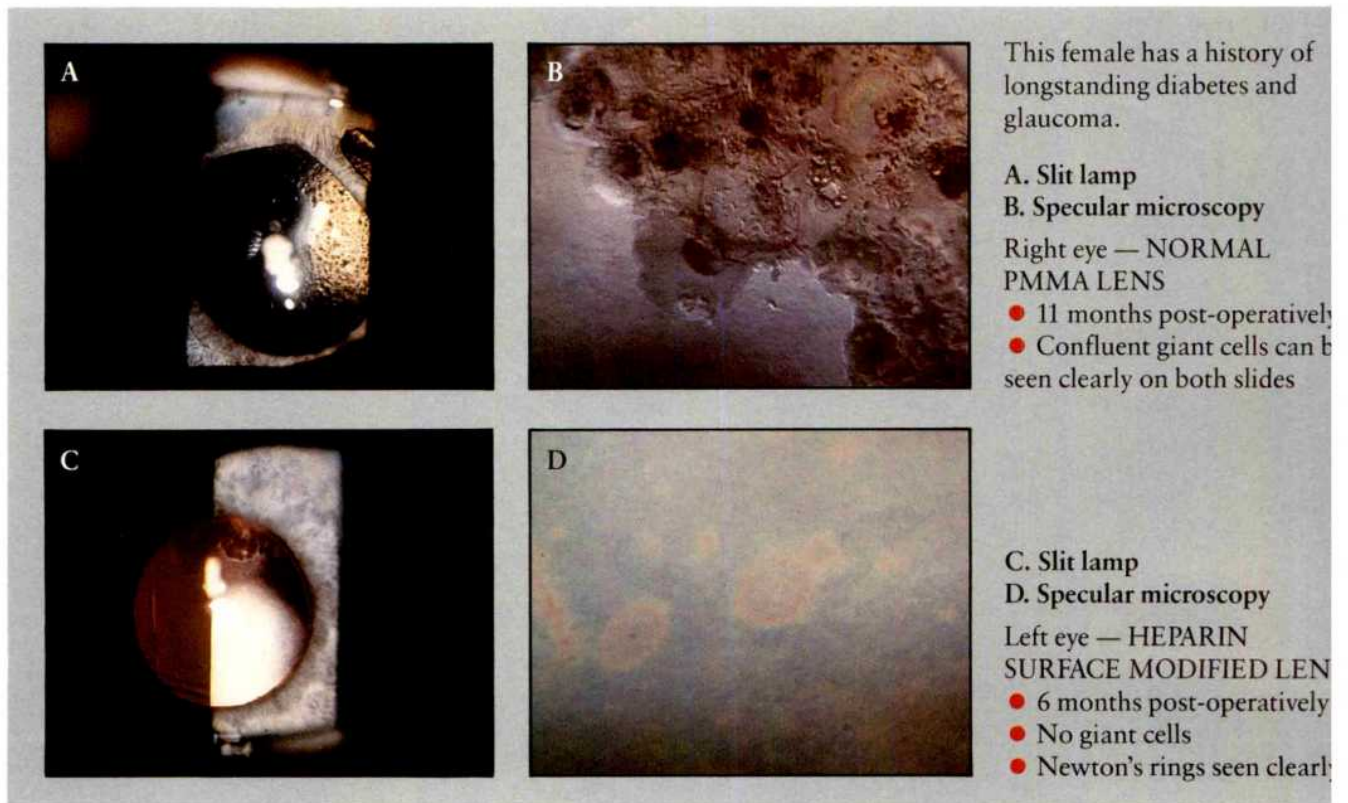
A CLEAR CHOICE IN THE GLAUCOMA EQUATION

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ALLERGAN PHARMACEUTICALS

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Laser photocoagulation control of diabetic macular oedema without fluorescein angiography

Ahmed M Abu El Asrar, Peter H Morse

Abstract

This study included 40 eyes in 22 diabetic patients with focal macular oedema. Laser photocoagulation was directed at decompensated or leaking microvascular lesions clinically detected without using pretreatment fluorescein angiograms. Post-treatment fluorescein angiograms performed after adequate clinical control of disease showed complete resolution of the macular oedema in 25 eyes (62.5%), whereas persistent leakage from microvascular lesions closer than 500 μ m from the centre of the foveola was noted in 15 eyes (37.5%). These were clinically detected during the pretreatment examination and were found not to impair or threaten the patient's vision. Our data confirm the clinical impression that fluorescein angiography is not necessary for effective treatment and should be used only if necessary.

The beneficial effect of photocoagulation for focal or diffuse diabetic macular oedema has been demonstrated.¹⁻⁷ In most studies fluorescein angiography was performed for pretreatment and post-treatment evaluation.³⁻⁷ However, it is our impression that routine fluorescein angiography is not necessary for effective treatment or adequate clinical control.

We undertook the study of diabetic patients who had focal macular oedema and were treated with argon laser to demonstrate that the majority of the patients could be satisfactorily treated without fluorescein angiography.

Patients and methods

This study comprised 40 eyes of 22 diabetic patients that had focal macular oedema and hard yellow exudates involving or threatening the fovea (Fig 1).

The patients were six men and 16 women whose ages ranged from 85 years to 34 years, mean 57 years. The diagnosis of diabetes had been made in these patients from age 4 to 53 years, average 19.7 years. Sixteen of them used insulin and six of them oral hypoglycaemic agents.

The pretreatment ocular examination consisted of best corrected visual acuity; slit-lamp examination; Goldmann applanation tonometry; examination of vitreous and retina by direct and indirect ophthalmoscopy and contact or non-contact lenses. During the initial examination care was taken to identify the leaking lesions. Decompensated or leaking microvascular abnormalities were clinically identified by means of the direct ophthalmoscope. Lesions which were characterised by transudation or extravasation were observed to be surrounded by oedema of the neurosensory retina, often with an irregularity of the internal limiting membrane light reflex. With a longer course of extravasation the decompensated retinal microvascular abnormalities were bordered by hard yellow exudates, or with a greater duration by cholesterol crystals. If treatment was indicated because of decompensation, other microaneurysms in the area which might later leak were also treated. Pretreatment fluorescein angiograms were performed but were not examined prior to or used during photocoagulation.

All microaneurysms and dilated capillaries, some of which were telangiectatic in areas of oedematous retina, were treated. The treatment was with the 50 to 100 μ m argon blue-green laser of 0.05 to 0.1 second duration, with adequate power to obtain definite whitening within the wall of the microvascular lesion. Care was taken to focus precisely at the level of the lesion to be treated. Repeated burns with adjustment of focus were usually needed to obtain actual whitening in the wall of the leaking lesion itself. Treatment of lesions closer than 500 μ m to the centre of the macula was not done initially if they were not affecting or threatening the patient's vision. When treatment of these lesions was indicated, a spot size of 50 μ m with a 0.02 to 0.05 second duration was used to minimise the size of the laser burn near the foveola.

Follow-up examinations identical to the pretreatment examination were performed every four to six weeks. Subsequent treatment was performed for lesions that had not been sealed during the initial treatment. Post-treatment fluorescein angiography was performed when it was determined clinically that the focal macular oedema was controlled.

The pretreatment and post-treatment fluorescein angiograms were compared for absence or persistence of leakage.

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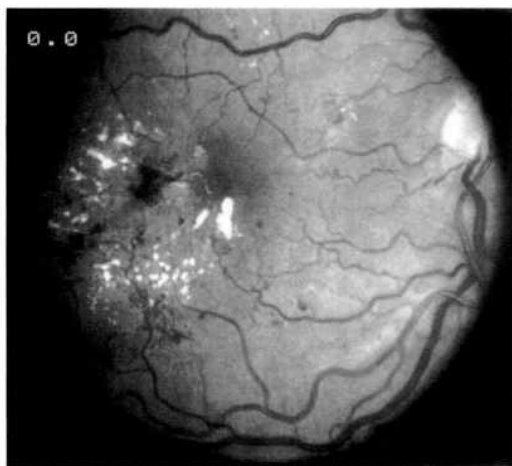


Figure 1 Pretreatment photograph of the right eye of a 54-year-old woman with diabetes mellitus of 15 years' duration, showing background diabetic retinopathy with decompensated microaneurysms and capillaries with a serous elevation of the neurosensory retina surrounded by hard yellow exudates encroaching on the foveola.

Figure 2 Fluorescein angiogram of the eye showing early hyperfluorescence of the microaneurysms and blockage of the fluorescence by haemorrhage.

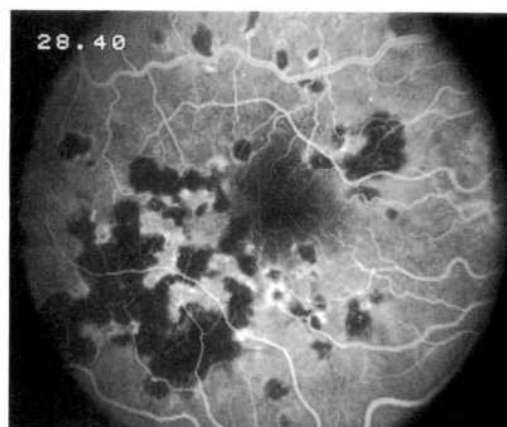
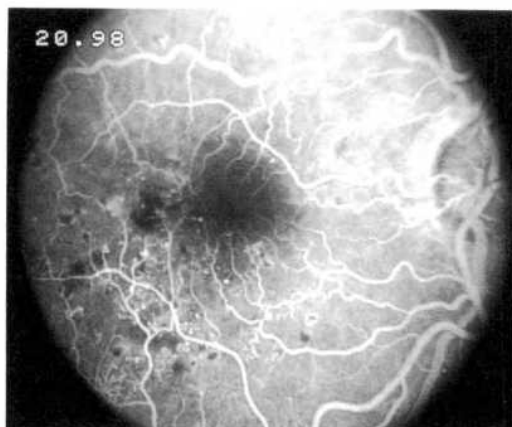


Figure 4 Four months post-treatment fluorescein angiogram of the eye showing that the leaking microvascular lesions have been effectively treated.

Results

The pretreatment fluorescein angiograms showed focal leakage from microvascular lesions in all the eyes included in the study (Figs 2 and 3). The pretreatment visual acuity was 20/20 to 20/30 in 20 eyes, 20/40 to 20/60 in nine eyes, 20/70 to 20/100 in six eyes, and 20/200 in five eyes. The average follow-up period was six months.

The post-treatment fluorescein angiograms showed complete resolution of the macular oedema in 25 eyes (62.5%) (Fig 4), while persistent leakage was noted in 15 eyes (37.5%) despite satisfactory clinical control of the disease.

In all these eyes the leakage was from microaneurysms closer than 500 μm from the foveola that were identified clinically during the pretreatment examination and at the time of treatment.

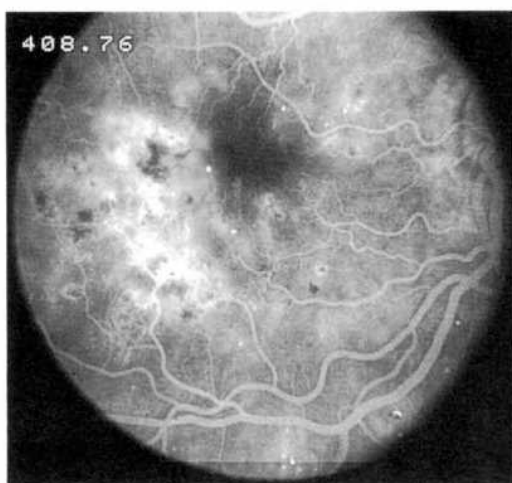
A change in vision by at least two lines on the chart was required to be considered better or worse. A change of one line was considered the same. At the final follow-up examination visual acuity was found to be improved in six eyes (15%) and unchanged in 34 eyes (85%). Among the improved eyes, the pretreatment visual acuity was 20/30 in one eye, 20/100 in three eyes, and 20/200 in two eyes.

Thirty eyes (75%) had single laser treatment and 10 eyes (25%) had two treatments.

Discussion

In this study 25 eyes (62.5%) showed complete

Figure 3 Late phase fluorescein angiogram of the eye showing extravasation of fluorescein dye round the leaking microaneurysms.



angiographic resolution of the focal macular oedema, whereas 15 eyes (37.5%) showed persistent angiographic leakage. This leakage was from microvascular lesions closer than 500 μm from the centre of the foveola, which were judged not to interfere with or threaten the patient's vision. On subsequent examinations there was a satisfactory clinical control of the disease. Complete resolution of macular oedema was achieved in only 3% of the treated eyes in a previous study because of microaneurysmal leakage too close to the fovea.⁵ In our cases treatment of lesions closer than 500 μm from the centre of the macula was undertaken only if they were impairing or threatening the patient's vision. With treatment of these lesions there is some risk of damaging the subfoveolar retinal pigmented epithelium or creating symptomatic scotomas.

Our data support the clinical impression that routine fluorescein angiography is usually not necessary for effective treatment and control of focal macular oedema. Microaneurysms and damaged retinal capillaries may leak plasma and be surrounded by oedema and hard yellow exudate. Careful ophthalmoscopy and contact or non-contact lens examination will reveal these foci of microvascular incompetence. Rarely, when leaking persists after photocoagulation or if there is an occult lesion, fluorescein angiography may reveal the refractory area. In patients with profound nuclear sclerosis, which decreases contrast and complicates the visualisation of microvascular detail, fluorescein angiography may be required to detect decompensated microvasculature. Moreover, in patients who had previous laser treatments, areas of chorioretinal atrophy may obscure leaking microaneurysms and require fluorescein angiography.

Background diabetic retinopathy may have several subcategories of classification. Although this study dealt with focal and multifocal patterns of macular oedema caused largely by decompensated microaneurysms, a diffuse telangiectatic pattern resulting from a widespread decompensated microangiopathy may also occur, prompting a more guarded prognosis. An ischaemic background retinopathy is not amenable to laser therapy. It should be empha-

sised that the prognosis also depends on the patient's co-operation and positioning of the head at the time of laser treatment.

During treatment it is of critical importance to focus the laser beam at the level of the microvascular lesion. The treatment may have to be repeated until a white reaction is seen within the wall of the microvascular lesion. It should be emphasised that multiple treatment sessions may be required to achieve adequate clinical control of the disease.

Finally our results show that fluorescein angiography is not absolutely necessary in planning and carrying out photocoagulation in diabetic eyes with focal macular oedema and should not be used routinely, but only if necessary.

- 1 Patz A, Schatz H, Berkow JW, Gittelsohn AM, Ticho U. Macular edema: an overlooked complication of diabetic retinopathy. *T Ophthalmology* 1970; 77: OP 34-42.
- 2 Multicentered Controlled Study. Photocoagulation in treatment of diabetic maculopathy. *Lancet* 1975; ii: 1110-3.
- 3 Blankenship GW. Diabetic macular edema and argon laser photocoagulation: a prospective randomized study. *Ophthalmology* 1979; 86: 69-78.
- 4 Townsend C, Bailey J, Kohner E. Xenon arc photocoagulation for the treatment of diabetic maculopathy: interim report of multicenter controlled clinical study. *Br J Ophthalmol* 1980; 64: 385-91.
- 5 Reeser F, Fleischman J, Williams GA, Goldman A. Efficacy of argon laser photocoagulation in the treatment of circinate diabetic retinopathy. *Am J Ophthalmol* 1981; 92: 762-7.
- 6 Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema: early treatment diabetic retinopathy study, report number 1. *Arch Ophthalmol* 1985; 103: 1796-806.
- 7 Olk RJ. Modified grid argon (blue-green) laser photocoagulation for diffuse diabetic macular edema. *Ophthalmology* 1986; 93: 938-48.

Injector for highly viscous silicone oil

Norbert Hausmann, Gisbert Richard

Abstract

A syringe device for the injection and evacuation of highly viscous silicone oil was developed. The problem of removing the air interfering with these manoeuvres was solved by providing special outlets in the plunger and handle of a conventional glass syringe. A slightly modified commercial motor perfusor was chosen to power this device, which has proved to be good and fail-safe in more than 100 cases.

The main types of silicone oil injected in complicated proliferative vitreoretinopathy cases after vitrectomy now have viscosities of 1000 and 5000 (highly purified) centistokes.¹ Owing to the high viscosity, an injection syringe can be filled properly only with its face down from behind after removal of the plunger; simple aspiration will not work. To evacuate the air, then located between oil level and plunger after reassembling the syringe, part of the silicone oil must be squeezed out – the syringe now faced upwards – together with the air locked in the entire system. This necessitates a considerable sacrifice of time and loss of oil. Further, owing to the high viscosity of the 5000 centistokes oil in particular, a strong and reliable motor which works in both directions is required, and which, besides injection, also ensures evacuation of oil in the same way. In our view there is no instrument on the market that meets these requirements at a reasonable price. We have therefore designed the instrument described below.

The instrument

To solve the problem of removing the air

between oil level and plunger we took a conventional glass syringe and bored through the centre of its plunger and handle. The cone of the plunger was changed, so that its top pointed then to the bore hole, where the air could now accumulate. Above the plunger a right-angled outlet was added laterally in the first third of the handle leading the bore out. To make this outlet tight we have slipped a movable concentric tube with an internal thread over the handle, which in its turn was provided with a corresponding external thread (Fig 1). The syringe is now filled from behind in the usual way when the plunger is removed. The plunger is then inserted with the concentric tube on its handle unscrewed and finally slid down to the oil level. In this way the air above the oil can accumulate in the plunger's cone and escape through the lateral outlet. When the syringe is void of air, the concentric tube is screwed down along the thread past the outlet. This makes the system airtight (Fig 1). Through a pressure-proof Teflon hose the silicone oil passes into the vitrectomised eye, either directly via the infusion line or through a blunt needle controlled by the surgeon's hand. The technique of fluid exchange has been described elsewhere.²

A syringe for silicone oil injection should no longer be manually operated by screwing a spindle, as earlier publications on this topic recommend.³⁻⁵ Commercial quality power sources are either battery operated and therefore susceptible to trouble or have a rather expensive mains connection.⁶ For these reasons we have chosen a time tested motor perfusor, which is at hand in every hospital for the precise control of thrombolysis by streptokinase to power our syringe. It was fastened to the perfusor by a cross bar at the tip and by a cone and a screw at the handle (Fig 2). The power of the perfusor will allow a choice among several speeds of injection, even for the highly viscous 5000 centistokes oil. The same applies, for example, to evacuation in a case of oil bubble behind the retina. Owing to the high suction power needed for this manoeuvre an increasing concentration of air in the syringe is unavoidable, even if the plunger has been ground in with the utmost precision. Therefore the plunger soon comes to a stop, leaving a mostly air filled and functionally disturbed syringe.

With our device removal of air during oil evacuation is as simple as is oil filling: The whole instrument is tipped down by a surgical nurse to accumulate the air again between the oil level and the plunger. The concentric tube on the handle is then unscrewed and the plunger slid forward again by the activated motor. Thus the air is squeezed out through the handle's outlet. As soon as the air has escaped and the tube is tightened, the evacuation can continue with a normally positioned instrument. During this manoeuvre the surgeon can keep the evacuation

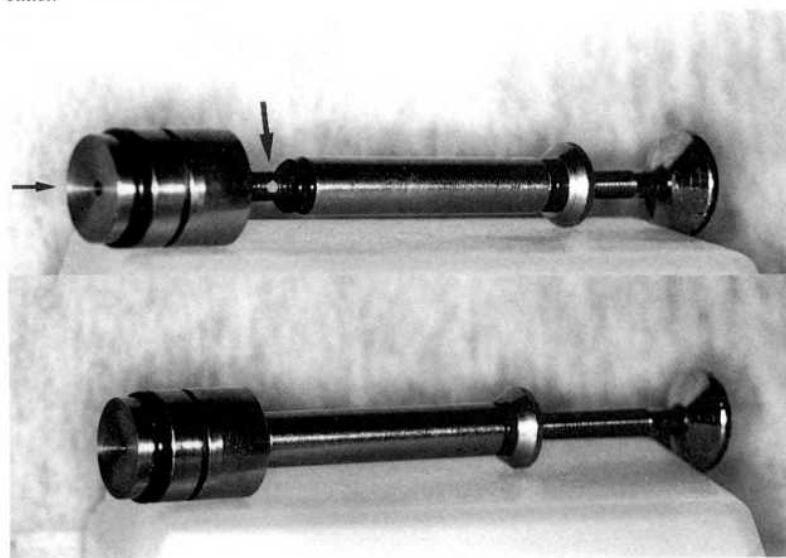
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Figure 1 Top: Inverse cone and borehole ground into the plunger, external thread and lateral outlet on handle (arrows), unscrewed concentric tube. Bottom: Tube screwed down along the thread past the lateral outlet.



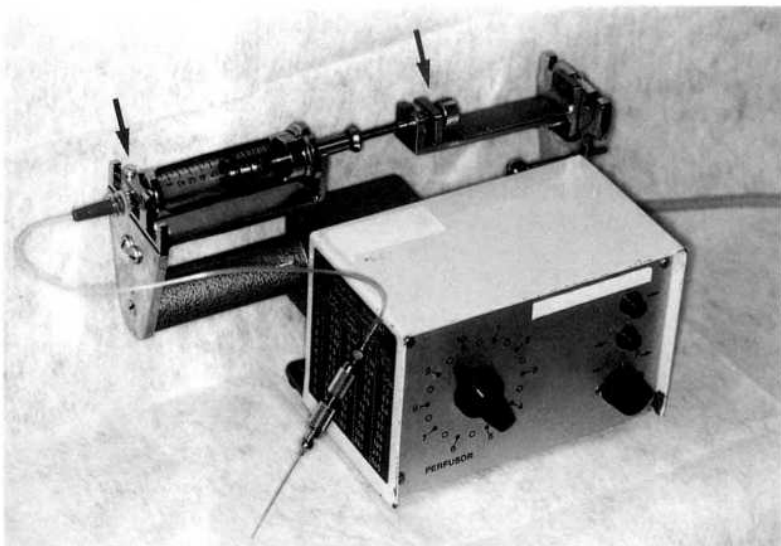


Figure 2 The oil filled, airless syringe fastened to the motor perfusor by a cross bar at the tip and by a cone and a screw at the handle (arrows).

needle in the eye. Thus he need not squeeze the air back through the complete system and the withdrawn needle.

The device described here is not commercially produced. It can, however, be made at a slight cost from supplies available at every hospital by any skilful mechanic. So far it has proved to be good and safe in more than 100 cases.

The authors have no proprietary or financial interest in the instrument. We acknowledge the constructional assistance and mechanical work done by our male nurse, Mr Djuro Bajic, at Feldkirch, Austria.

- 1 Gabel VP, Kampik A, Gabel C. Silicone oil with high specific gravity for intraocular use. *Br J Ophthalmol* 1987; 71: 143-8.
- 2 Charles S. Fluid-gas exchange in the vitreous cavity. *Ocutome Newsletter* 1977; 2: 1-3.
- 3 Gibis PA, Becker B, Okun E, Canaan S. The use of liquid silicone in retinal detachment surgery. *Arch Ophthalmol* 1962; 68: 590-9.
- 4 Kelly TSB. Screw type syringe for intravitreal injection. *Mod Probl Ophthalmol* 1969; 8: 577-80.
- 5 Scott JD. Treatment of detached immobile retina. *Trans Ophthalmol Soc UK* 1972; 92: 351-7.
- 6 Zivovnovic R. *Silicone oil in vitreoretinal surgery*. Lancaster: Kluwer Academic, 1987: 25-7.

Outcome of cataract surgery in Central India: a longitudinal follow-up study

A Reidy, V Mehra, D Minassian, S Mahashabde

Abstract

An epidemiological follow-up study of patients who had intracapsular cataract extraction in a voluntary hospital and its associated eye camps in Central India has for the first time evaluated the outcome one year after surgery in terms of visual acuity, use of spectacles, and improvement in income and mobility. The findings indicate that under these fairly typical conditions, 92% of the cases have adequate vision of 6/18 or better one year after surgery. Information on high usage of spectacles and on considerable improvements in income and mobility after cataract surgery is also reported. The outcome for patients operated upon in eye camps was almost as favourable as for those operated upon in hospital. Although the small differences are not statistically significant, the comparative findings require cautious interpretation and give rise to the epidemiological issues which are briefly discussed in this paper.

It is estimated that approximately 1 million intracapsular cataract extractions are performed in India¹ each year, some in hospitals and a considerable number in eye camp facilities such as temporarily used schools and meeting halls. Yet nowhere in the ophthalmic literature is there a report of an epidemiological evaluation of the outcome of any of that surgery.

This paper reports the results of a study carried out from 1987 to 1989 in Raipur, Madhya Pradesh, in which patients were interviewed systematically and examined before surgery and then again a minimum of one year after the operation. The aim was to determine visual outcome of surgery in a hospital and four of its rural eye camps. It was also hoped to find information on the patients' use of aphakic spectacles and any changes in income and mobility due to regained sight.

Patients and methods

Patients were chosen for the study sequentially as they presented themselves during the recruitment period, and there were very few refusals. More patients were recruited from the four eye camps than from the hospital (ratio 5:1) to reflect the proportion of rural outreach-work to work at the hospital. This type of work load is typical of many voluntary hospital associations in India.

BASELINE ASSESSMENT

A full eye examination by standardised methods was carried out before surgery. It included measurement of visual acuity with glasses if worn

and pinhole examination, funduscopy through the dilated pupil, and examination of the anterior segment of the eye with an illuminated magnifying loupe. A questionnaire on patient's income and mobility was administered by a trained survey worker.

OPERATIVE PROCEDURES

The surgical procedure adopted was a standard intracapsular cataract extraction under a magnifying loupe and with a minimum of three sutures. Conditions in eye camps and hospital were typical of similar well established voluntary health provisions in India. The surgeon in charge was a very experienced cataract surgeon.

Any complications during surgery were recorded, as were any necessary deviations from the standard routine of the surgical procedure. Postoperative assessment before discharge included recording of any complications and also refraction.

FINAL ASSESSMENT

Between 12 and 13 months after surgery each patient was located again and re-examined and interviewed. This was done in the home or neighbourhood of the patient in both the urban and rural areas.

Every effort was made to find the patients one year after surgery. This often meant visiting the patient's home in hard-to-reach rural areas more than once. None were lost to the study other than those who died. Ascertained information about use of glasses and improvement in mobility and income were confirmed through detailed interviews with relatives.

ASSESSOR AND ANALYSIS

An independent assessor (an in-state ophthalmic surgeon trained in basic epidemiology) was employed to monitor the fieldwork and to report on quality control.

The data were recorded on specially designed proformas, entered into a computer relational database in the hospital, and analysed by software developed at the International Centre for Eye Health at the Institute of Ophthalmology.

Results

Out of a total of 600 patients 547 were operated on by the same experienced ophthalmic surgeon. Surgery for the remaining 53 patients was shared among four other surgeons, so these cases are excluded from this report. Of the 547 patients included in the study 50 died during the follow-up period, leaving 497 patients. All of these were

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Table 1 Age and sex distribution of the patients

	Age groups						Totals
	<40	40-49	50-59	60-69	70-79	80+	
Males	4	13	49	116	31	8	221
Row %	1.81%	5.88%	22.17%	52.49%	14.03%	3.62%	100.00%
Total %	0.73%	2.38%	8.96%	21.21%	5.67%	1.46%	40.40%
Females	8	19	65	181	46	7	326
Row %	2.45%	5.83%	19.94%	55.52%	14.11%	2.15%	100.00%
Total %	1.46%	3.47%	11.88%	33.09%	8.41%	1.28%	59.60%
Total	12	32	114	297	77	15	547
Row %	2.19%	5.85%	20.84%	54.30%	14.08%	2.74%	100.00%

successfully located and assessed one year after surgery.

No patient had an operation on the second eye within six months of the operation on the first. If the patient had surgery on the second eye within the year, this was not counted in the follow-up for evaluation purposes.

The age and sex distributions of the 547 patients who had surgery are shown in Table 1, where it can be seen that there were more females (326) than males (221) and that the largest number of patients for both sexes was in the 60-69 year age group. The patients operated on in eye camps were somewhat older than those operated on in hospital. The proportion of patients aged 60 years and older was 64% in the hospital operated cases and 73% in those operated on in eye camps.

Eighty-two persons had the operation performed in hospital and 415 in eye camps. This reflects to a great extent the workload of that type of voluntary hospital in Madhya Pradesh.

VISION ONE YEAR AFTER SURGERY

In four of the 497 surviving patients operated on by the same surgeon the exact visual acuity was unavailable at the time of data analysis leaving 493 cases fully documented.* Nine of these had preoperative complications such as corneal opacities or optic nerve damage from glaucoma and were not expected to show substantial improvement in vision after surgery. This left 484 surviving patients who had surgery and were expected to have adequate vision one year after surgery.

About 92% of these 484 patients (443 patients)

*These were cases where the illegible handwriting of the examiner could not be recorded. All other aspects of the ophthalmological examination and responses to the other questions showed that none of these patients were blind or visually impaired in the operated eye.

Table 2 Vision in the operated eye, one year after cataract surgery, by age. Comparison between hospital and camp operated cases

Age		Vision in operated eye				Total
		6/18 or better	6/24 to 3/60	Blind <3/60	Worse than 6/18	
0-59	Hospital	32	0	1	1	33
	%	96.97	0	3.03	3.03	
60+	Camp	112	2	4	6	118
	%	94.92%	1.69	3.39	5.08	
All Ages	Hospital	43	3	1	4	47
	%	91.49	6.38	2.13	8.51	
	Camp	256	15	15	30	286
	%	89.51	5.24	5.24	10.49	
	Hospital	75	3	2	5	80
	%	93.75%	3.75	2.50	6.25	
	Camp	368	17	19	36	404
	%	91.09	4.21	4.70	8.91	
	Totals	443	20	21	41	484
	%	91.53	4.13	4.34	8.47	

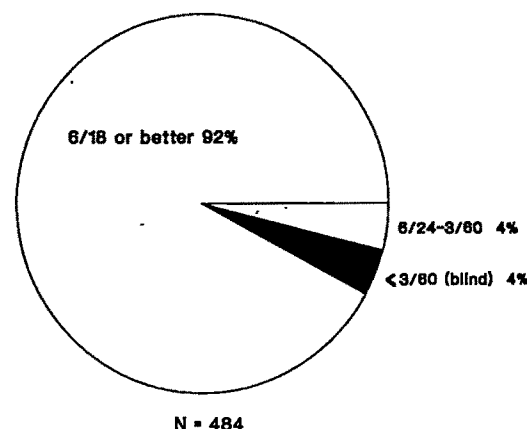


Figure 1: Corrected vision in the operated eye one year after surgery.

had a corrected vision of 6/18 or better (95% confidence limits 89%-94%). A further 4.13% (20 patients) had vision of between 6/24 and 3/60. The remaining 4.3% (21 patients) had vision of less than 3/60 in the operated eye. The details are shown in Table 2 and Fig 1.

When the vision in the non-operated eye was taken into account, the group of postoperative blind was reduced to 2.4%.

We are here using the World Health Organisation categories of <3/60 as blind, 3/60 to <6/18 as visually impaired (low vision, and 6/18 and above as adequate vision.)

CAMP AND HOSPITAL

The visual outcomes in the eye camp and in the hospital are compared in Table 2. Successful outcome (vision 6/18 or better in the operated eye) was 91% in the eye camp operated cases and 94% in the hospital operated cases. The corresponding unfavourable outcomes (less than 3/60 after surgery) was 2.5% for the hospital and 4.7% for the eye camp cases. The difference between eye camp and hospital was not statistically significant ($\chi^2=0.8$, d f=2, p=0.66).

If postoperative vision of <6/18 is taken to indicate unsatisfactory outcome, the incidence of this outcome was 6.25% in the hospital patients and 8.91% in the camps - a difference of 2.66%. When age is taken into account the percentage differences in outcome between hospital and camp were somewhat reduced, namely, 2.05% in the younger age group (0-59 years) and 1.98% in the older age group (60+ years). The details are shown in Table 2.

When age is taken into account for those operated cases with vision of <3/60 the difference between hospital and camps within the 0-59 year age group is reduced to a trivial 0.36% (Table 2).

PATIENTS VIEW OF THE OUTCOME OF CATARACT SURGERY

Improvement in eyesight

The patients' view of the improvement in sight after surgery was similar to the ophthalmological assessment. Of the 497 patients operated on by the same surgeon 453 (91.15%) thought that the operation had improved their vision. Another 5% thought that their vision was similar to its

Table 3 Improvement in income one year after cataract surgery (successfully operated cases)

	Age Groups			Totals
	<50	50-59	60+	
Males				
Total	17	44	116	177
Improved	13	29	69	111
% improved	76.47	65.91	59.48	62.71
Females				
Total	23	60	183	266
Improved	23	38	91	152
% improved	100.00	63.33	49.73	57.14
Males+females				
Total	40	104	299	443
Improved	36	67	160	263
% improved	90.00	64.42	53.51	59.37

preoperative state, and only 3% thought matters were worse.

Provision and usage of spectacles. Of the 497 postoperative cases 483 (97%) had been given glasses. The remaining 14 patients claimed that they had not received glasses and/or had promised to make their own arrangements for glasses but had failed to do so.

Of the group (483) who had been given glasses 65 patients (13%) did not use them, but the other 418 (87%) claimed to be wearing them regularly. Of this latter group 12 (3%) found the spectacles uncomfortable and in most cases this was claimed to be due to spectacle induced double vision.

Improvement in income. When asked about improvement in income 59% of the successfully operated patients claimed to have an improvement in income as a direct result of being able to see better after the operation. Figures for the camp and the hospital on this issue are similar. More males than females had an improvement in income, 62.7% as against 57.1%. However, this is not a startling difference and disguises some age group variation. All the females (23) in the under 50 year group claim an improvement in income compared with 76% (13) of the males in this age group. These findings are shown in Table 3.

Improvement in mobility, housework, and yard work. When questioned on mobility 95% of those operated on in hospital and 92.7% of those in eye camps claimed to have the advantage of increased mobility as a direct result of the improved sight from the operation. In the camp there were 10 cases where this information was incomplete or missing.

Housework. From the reaction of the males to this question at the pilot study stage we considered that in the main study we would ask these questions only of the females. After surgery 98.4% of the females considered that they had an improvement in their ability to do housework, and this considerable improvement was true for all age groups.

Yardwork. For the work outside the home but not directly related to income, such as yard cleaning and drawing fuel and water, all the males and 98% of the females claimed to be more competent at this and to be able to do more of it.

Perception of these factors before and after surgery. Interestingly the patients' perception of how their income and mobility were affected when their eyesight was poor owing to cataract was somewhat out of line with the advantages they claimed one year after surgery.

When again we consider successfully operated cases only and look at the perceived changes in income, we find that before the operation 71% of males thought that poor eyesight due to cataract did not affect their income or chances of earning some or more income. One year after the operation 52% of this group claimed that there was an improvement in their income owing to restored vision. In the case of females it was 63% who thought their income was unaffected by poor eyesight before the operation, and 49% of this group claimed to have an improvement in income on year afterwards.

Mobility. No male admitted to reduced mobility before the operation, but 77% claimed to have improvement in mobility afterwards. For women the figures in this case were 2% and 83% respectively.

Discussion

The primary aim of this study was to evaluate the visual outcome of cataract surgery one year after it had taken place in a typical voluntary ophthalmic service facility which had a good coverage of rural and urban populations in India and a substantial commitment to outreach surgical work in eye camps. A secondary aim of the study was to allow some fairly crude comparison of results between hospital and camp operated cases. For a comprehensive comparison a much larger study would be required whereby most of the suspect or possible prognostic factors largely concerning the patient and her/his home environment would be analysed simultaneously through logistic linear modelling so that a 'fairer' comparison with minimal confounding could be made. In our estimation, based on costs of this present study, such a comprehensive study would cost £100 000 and require a level of co-operation from elderly patients and their families which might deter many from coming for surgery, especially in rural areas.

When hospital and camp operations were compared, there was no significant differences between them in unfavourable outcome, (blindness, vision less than 3/60 in the operated eye one year after surgery). This does not necessarily mean that there is in fact no difference at all in the unfavourable outcome rates. Small differences would have less than a reasonable chance of being detected as significant in the study. However, if there was in fact a substantial difference, the study would have a good chance of detecting it as significant. For example, on the assumption that the unfavourable outcome was 2.5% in the hospital operated cases, and the unfavourable outcome was 10% or more in camp patients (that is, a difference of 7.5% or more), then the study would have a power of at least 90% (90%+ chance) of detecting the difference as statistically significant. The findings therefore indicate that the difference in unfavourable outcome is likely to be less than 7.5%.

Some of the observed difference in unfavourable visual outcome between hospital and eye camp could be explained by the higher proportion of elderly persons operated on in the camps. Thus age can be seen as a confounder. Diabetes could have been another possible confounder.

However, the sample did not include any known diabetics, and all the patients had routine urine sugar tests.

We can conclude that in skilful hands and with experienced and organised teams surgery in eye camp facilities such as schools and similar accommodation can give results comparable with surgery in a relatively well equipped hospital in similar circumstances in the same region of India.

The outcome of cataract surgery in other locations in India may be worse or possibly better than the findings reported in this study. There are no comparable published data that are based on sound epidemiological methods ensuring unbiased patient selection and complete or near complete follow up with minimal or no bias in ascertainment of the outcome one year after surgery.

Clearly the selection of patients for inclusion in a study of this kind should be random or sequential without bias and should span a reasonable period of time. Similarly, in order to minimise bias the outcome of surgery should be

ascertained by adequately trained personnel (other than the surgeons who performed the operations) with systematic and consistent use of standardised methods of examination and/or interview. An independent assessor such as was employed in this study is of considerable importance. A common problem is incomplete follow-up – for example, less than 95% – which could easily give rise to large bias resulting in gross underestimates of poor outcome after surgery.

If data from other investigations are to be compared with the findings of this study it is essential to scrutinise the methodological base of these data and to ask how and to what extent the aforementioned sources of bias were dealt with.

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1 Venkataswamy G. Ophthalmology in India, *Arch Ophthalmol* 1989; 107: 931–2.

Recovery of the blood-aqueous barrier after cataract surgery

V M G Ferguson, D J Spalton

Abstract

Following extracapsular cataract and posterior chamber implant surgery the sequential recovery of the blood-aqueous barrier was measured by anterior segment fluorophotometry. Postoperatively 49 (69.0%) out of 71 eyes (71 patients) had recovered at a uniform rate, re-establishing a normal blood-aqueous barrier by the end of the three-month study. In these eyes recovery of the blood-aqueous barrier was unaffected by the use of preoperative indomethacin, the surgeon, the type of section, or the type of fixation of the implant. In eyes recovering normally after cataract surgery the rate of recovery of the blood-aqueous barrier can be expressed by a in the equation $a=(y-b)/x$, in which y is the logarithm of the anterior chamber fluorescence, x is the time after surgery, and b is a constant for each patient which is the anterior chamber fluorescence measured immediately after surgery. This normal rate of recovery provides a baseline from which to assess surgical technique or postoperative medication.

The results of cataract surgery and visual recovery vary in the postoperative period, but in the long term they are highly successful, with vision of 6/12 or better in over 95% of patients. Failure in otherwise normal eyes is related to poor placement of the implant, residual soft lens matter, posterior capsular thickening, uveitis from surgical trauma or chronic chafing of uveal tissue, low grade infection, or cystoid macular oedema. Breakdown of the blood-ocular barriers (both the blood-aqueous barrier anteriorly and the blood-retinal barrier posteriorly) may occur in these conditions and has been implicated in the pathogenesis of many of these problems.^{1,2}

Anterior segment fluorophotometry is an objective, reproducible, and simple technique³ for measuring the degree and duration of breakdown of the blood-aqueous barrier (BAB) and was used in this study to follow the sequential recovery of the BAB in 71 patients for the first three months after surgery, with the aim of studying the factors that influence the immediate postoperative recovery of the eye following routine extracapsular cataract extraction and insertion of a posterior chamber implant.

Material and methods

Approval was obtained from the West Lambeth Health Authority Ethical Committee for this study. Patients had no severe cardiovascular or respiratory disease or severe allergy and were willing to co-operate with intravenous fluorophotometry. There were 71 patients (71 eyes

studied) of which 28 were males and 43 females (58 Caucasian, 10 Negro, 3 Asian), and all were aged between 43 and 81 (mean 66.4 years, SD 9.4). Extracapsular cataract surgery with insertion of a posterior chamber implant was carried out by three experienced surgeons, each performing his routine technique, the differences between them being in position of the section and fixation of the implant (either in the ciliary sulcus or in the capsular bag). Patients were not on any topical or systemic anti-inflammatory drugs prior to surgery apart from those prescribed preoperative topical indomethacin, and no subconjunctival steroids were given after surgery. The operative details recorded were the surgeon, the type of section, the position of the implant (either in the ciliary sulcus or in the capsular bag), and the amount of trauma, if any, to the iris.

Within seven days of surgery and at one, two, and three months postoperatively a record was made of the clinical findings, and anterior segment fluorophotometry was performed. All patients received fluorescein from the same batch to avoid manufacturing variations in available fluorescence. Fluorescein angiography was performed (sodium fluorescein 20% w/v, 14 mg/kg, intravenously) so that optic disc leakage and angiographic cystoid macular oedema could be recorded, and one hour later anterior chamber fluorophotometry scans were made with the Fluorotron Master (Coherent Radiation). The fluorophotometer measures anterior chamber (AC) fluorescence as the fluorescence of an equivalent concentration of free fluorescein in ng/ml (=µg/l).

The normal level of AC fluorescence for eyes with intact BABs was defined from our other

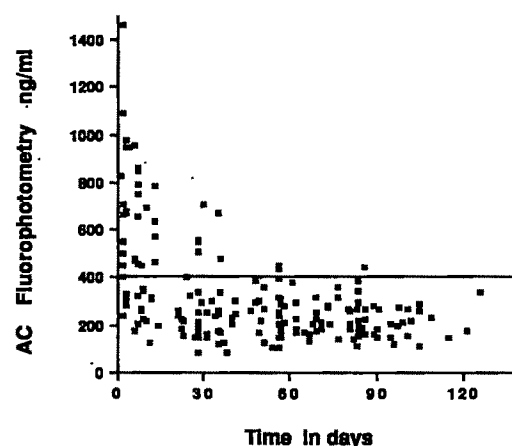


Figure 1 Scatter graph of AC fluorescence with time for all 49 eyes which recovered unevenly. There are high levels immediately after surgery, which fall during the first month. At three months 69% of eyes had levels of AC fluorescence below 400 ng/ml (µg/l).

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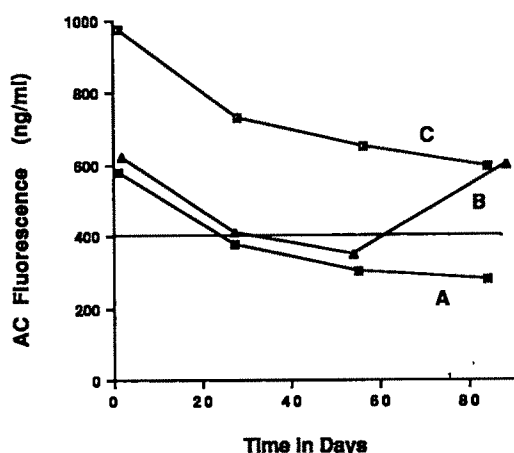


Figure 2 AC fluorescence falls with time, shown by the results from three patients. A has recovered normal levels of AC fluorescence by three months. B appears to recover initially but has an unexpected rise in AC fluorescence at three months. C continues to have prolonged breakdown throughout the study. (Horizontal line indicates upper limit of normal leakage, 400 ng/ml= μ g/l.)

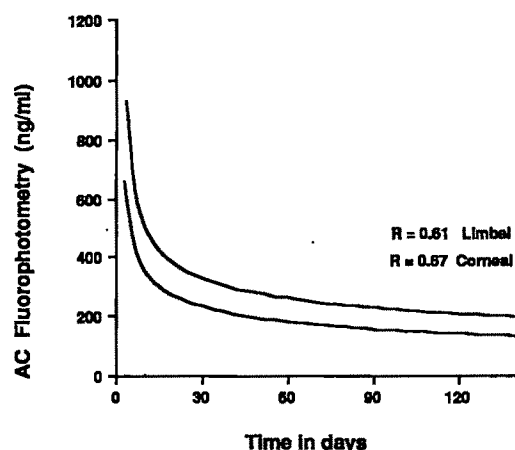


Figure 3 Rates of recovery of the eyes with limbal compared with corneal sections, shown by the change in AC fluorescence with time after surgery. R =coefficient of correlation for the best-fit curve through the data for limbal and corneal groups. Immediately after surgery the group with limbal sections have higher anterior segment leakage, but at three months both groups have re-established normal BABs. (ng/ml= μ g/l.)

work on healthy volunteers of the same age as those in the cataract study (36 eyes, mean age 61 years). In that study a mean AC fluorescence of 301 ng/ml (± 108 mean SD) with a range of 140 ng/ml to 560 ng/ml ($=\mu$ g/l) was measured one hour after giving intravenous sodium fluorescein 14 mg/kg. In this study, because we were interested in those with normal recovery, patients were taken to have re-established normal BABs by three months if the final fluorophotometry reading was less than 400 ng/ml (therefore excluding those with excess leakage).

The 49 patients with normal recovery of the BAB were divided into groups according to the operating surgeon, the type of section (limbal or corneal), the position of the implant (sulcus or bag fixation), and whether topical indomethacin was used.

Results

The trend was for high leakage of fluorescent metabolites into the AC during the first post-operative week, with a steady fall in AC fluorescence during the following three months. By this time 49 eyes out of the total of 71 (69.0%) had normal levels of AC fluorescence below 400 ng/ml (μ g/l) (Fig 1). Of the remaining eyes 14 (19.7%) still had high levels at three months and 8 (11.3%) recovered initially, but subsequently had high levels. Typical examples are illustrated in Figure 2. The reasons for failure to recover the BAB in these patients are the subject of a subsequent report.

Sequential fluorophotometry measurements of the 49 eyes which had re-established intact blood-aqueous barriers were interpreted by calculating the rate of recovery of each patient. This was represented mathematically by the gradient a of the line $y=ax+b$, where y was the AC fluorescence on a logarithmic scale and x the time in days after surgery. There was a good correlation between the AC fluorescence and time for surgery when the best-fit linear graph was drawn through the four fluorophotometry measurements for each of the 49 patients. The mean

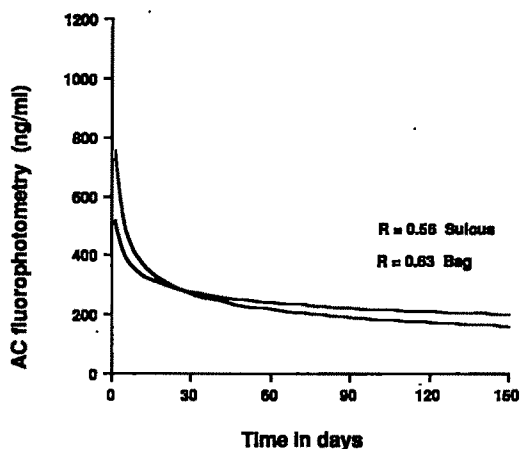
correlation coefficient for all 49 patients was 0.72 (SD 0.27). This mathematical expression of the recovery of eyes following surgery demonstrated that the BAB recovered to normal in a linear fashion.

These 49 patients were analysed further by grouping them so that comparisons could be made between the rate of recovery of eyes operated on by different surgeons and using different surgical techniques. Statistical comparison of the groups of patients was made by the Mann-Whitney U test.

The first two groups compared were those with sulcus placed implants but operated on by two different surgeons (Fig 3). Group A (nine eyes by surgeon 1) had a limbal section and group B (11 eyes by surgeon 2) had a corneal section. There was no statistically significant difference between the two groups (Mann-Whitney U test, $p>0.1$). There was a tendency for the eyes with limbal sections to have slightly higher levels of AC fluorescence initially, but at three months there was no significant difference between them. Apart from the type of section, both surgeons used similar techniques and the eyes showed comparable postoperative progress, final visual results, and final recovery of the blood-aqueous barrier, so all 20 eyes from these two surgeons were grouped as the 'sulcus group'.

The sulcus group and those with bag fixation of the implant (15 eyes by surgeons 1 and 2) were compared (Fig 4). Best fit curves show similar rates of recovery, falling to within 400 ng/ml (μ g/l), indicating recovery of the BAB by three months. The eyes with implants in the capsular bag had lower leakages initially ($p>0.1$) but by three months they had a slightly higher AC fluorescence than those with sulcus fixed implants, but this was not statistically significant (Mann-Whitney U test, $p>0.1$). Figure 5 shows the results of those with bag fixed implants, one group had no indomethacin (15 eyes by surgeons 1 and 2), and the other was treated with topical indomethacin preoperatively (11 eyes by surgeon 3). There was no significant difference between the mean rate of recovery for each group (Mann-Whitney U test, $p>0.1$).

Figure 4 Rates of recovery of eyes comparing implant fixation. R =coefficient of correlation for the best-fit curve through the data for sulcus and bag groups. Initially those with sulcus fixation have greater AC leakage than those with bag fixation, but at three months there was no statistically significant difference between them. (ng/ml= μ g/l.)



Analysis of the individual slopes of recovery did not show any evidence that the rate of recovery varied between the 49 eyes. The mean gradient was -0.004 (SD 0.003). That is, the eyes that recovered to normal all recovered at the same rate, the duration to recovery being solely determined by the degree of initial damage to the BAB (Fig 6).

Discussion

In cataract surgery the blood-aqueous barrier, which consists of the endothelium of iris blood vessels and the non-pigmented ciliary epithelium, is susceptible to surgical trauma at the time of operation, and this damage can either lead to recovery quickly or be prolonged for weeks or months after surgery. Several authors have looked at recovery of the BAB after cataract surgery, but this is the only sequential study of recovery of a cohort of patients with time. This report looks at those eyes (69%) which recovered a normal BAB within three months and at whether the speed of recovery was influenced by factors such as a limbal or corneal section, position of the implant in the bag or ciliary sulcus, the use of preoperative topical indomethacin, or the operating surgeon. We found no difference in the rate of recovery of the BAB in the first three months postoperatively from any of these factors.

Recovery of the BAB has been followed by iris angiography, which gives a qualitative assessment,⁴ but anterior segment fluorophotometry enables a quantitative measure of recovery of the BAB. There are various ways of interpreting the data from the fluorophotometer. Miyake *et al*⁵ used ratios comparing the aqueous

Figure 5 Comparison of the rate of recovery of eyes with and without preoperative topical indomethacin (all with bag fixed implants). R =coefficient of correlation for the best-fit curve through the data for each group. There is no statistically significant difference between them. (ng/ml= μ g/l.)

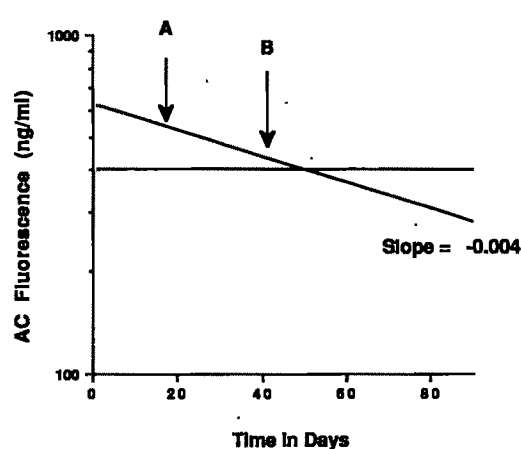
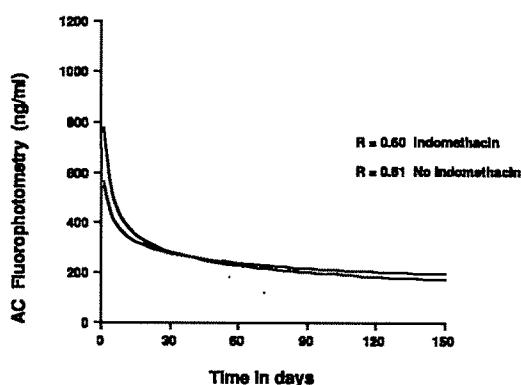


Figure 6 Normal eyes recover their BAB in a linear fashion despite different amounts of surgical damage to the BAB, provided their subsequent recovery is uneventful. For example, if a patient had BAB damage (A) postoperatively, the eye would take longer to recover than a patient with less damage (B), because the rate of recovery is the same for both of them. The slope for recovery is linear, so only one measurement is needed postoperatively to predict the time for normal restoration of the BAB. (ng/ml= μ g/l.)

fluorescein concentration in the operated eye to the aqueous fluorescein concentration in the fellow eye. Sanders *et al*⁷ looked at the pre- and postoperative levels and compared the percentage change in aqueous fluorescence in the operated eye with that in the fellow unoperated eye. Leisegang *et al*⁶ calculated the ratio of aqueous to plasma fluorescence after giving oral fluorescein to produce an index of BAB function. Sawa *et al*⁷ compared ratios of aqueous to plasma fluorescence after giving intravenous fluorescein to produce an index of BAB function. Araie *et al*⁸ calculated the transfer coefficient of diffusion after giving intravenous fluorescein, and Menerath *et al*⁹ calculated a transfer coefficient after giving oral fluorescein.

There are potential problems with all of these methods of measuring recovery of the BAB. The consensual response to surgery, in which there may be breakdown of the BAB in the fellow eye,¹⁰ means that the fluorescence measured in the fellow, unoperated eye cannot be used as a normal level against which to compare changes in the operated eye. Comparisons between pre- and postoperative measurements are complicated by the glare effect from autofluorescence of the cataractous lens. This artefact disappears when the cataract has been removed and an implant inserted (implants do not autofluoresce).

In order to calculate indices of permeability or diffusion assumptions have to be made, firstly, about fluorescein metabolism and its pharmacokinetics in the blood and in the eye (there are varying amounts of free and protein bound fluorescein and fluorescein glucuronide); and, secondly, the eye is taken as standard with spherical surfaces, a given area of iris and a given AC volume. These physiological formulae are not always valid in real patients, particularly in the inflamed eye. We took the plateau levels of AC fluorescence which we have done in previous studies³ (Ambrose VMG, *et al*, personal communication). They are simple to measure, with a reproducibility of 87% (comparing measurements on the same subjects on two separate visits, the nested analysis of variance showed an

intrapair correlation coefficient of $r=0.871$), and they provide an absolute measure of the degree of breakdown of the BAB which can be compared between patients.

In eyes with uncomplicated surgery we found that the BAB recovered rapidly during the first six weeks, and at three months a normal intact blood-aqueous barrier was demonstrated by stable plateau levels of AC fluorescence in 69.0% of eyes. But 31% of eyes failed to re-establish normal BABs. These included 19.7% (14 eyes) which still had high AC levels at three months and 11.3% (eight eyes) which appeared to recover normally at first but then had abnormally high levels. Interestingly, this proportion correlates well with the histopathological findings by Champion *et al*¹¹ who found that 34% of post-mortem eyes examined between eight months and 10 years after implant insertion showed evidence of cyclitis and iritis, and it suggests that inflammatory processes underlie failure to recover BAB function in most cases.

Other workers have also looked at the duration of breakdown and influence of implant position on recovery of the BAB. Sanders *et al*² showed that in eyes with uncomplicated surgery and postoperative subconjunctival and topical steroids the BAB was re-established by three months after surgery. Sawa *et al*⁷ used an index of BAB function in the early postoperative period (six days after operation) and found that insertion of a posterior chamber implant caused no increase in breakdown of the blood-aqueous barrier in comparison with eyes with extracapsular extraction without any implant. In a French study Menerath *et al*⁹ gave oral fluorescein, calculated a transfer coefficient, and found no difference in BAB dysfunction with and without an AC implant after intracapsular cataract surgery. They also gave oral piroxicam before and after surgery and found reduced BAB breakdown three days after surgery but no difference at two months in comparison with an untreated group. These results suggest that, in normal eyes with uncomplicated surgery, recovery of the BAB in the initial postoperative period is not influenced by either the presence or absence of an implant or its position in the bag, sulcus, or anterior chamber and that the changes in the BAB reflect a normal healing and recovery process in the iris and ciliary body.

While in the short term implant fixation may be unimportant in terms of recovery of the BAB, in the longer term there may well be significant implications. Miyake *et al*^{5,12} looked at eyes with uncomplicated extracapsular cataract surgery (average follow-up of one year after operation) and found that for posterior chamber implants those with sulcus fixation leaked more than those with bag fixation. They also showed that eyes with bag fixed implants had comparable leakage to eyes without implants. After a longer follow-up of three years there was no difference in the leakage between aphakic eyes and those with bag or sulcus implants. These results imply that the advantage of bag to sulcus fixation is the prevention of uveal chafing or erosion, which becomes obvious or important only on medium to long term follow-up.

In any study comparing the advantages of bag

to sulcus fixation of the implant in the posterior chamber it is necessary to know that the implant is actually where the surgeon intended to put it. In reality it is extremely difficult to assess this accurately, particularly when 7 mm diameter implants are used, as it is not easy to be certain that the implant is in the bag. It may be difficult to dilate the pupil to greater than this diameter, and even if the optic is contained in the capsule the haptics may have slipped out or eroded through it. In a post-mortem study Champion *et al*¹¹ and McDonnell *et al*^{13,14} looked at 65 post-mortem eyes. Only 5% of eyes had both loops in the capsular bag, 54% had one loop in the bag, and 42% had both loops out of the bag. Of the eyes with only one loop in the bag, 77% had the lower loop in and 23% had the superior loop in the bag. Overall, they found that erosion of the ciliary body was related to the size of the implant and elasticity of the haptics rather than the surgical placement or the length of time the implant had been in the eye. From this work one must accept that there must be unavoidable doubts about the true site of implant fixation in any clinical study unless the ciliary body itself can be directly visualised.

Topical treatment with indomethacin preoperatively (one drop twice daily for two days preoperatively) did not appear to influence recovery of the BAB. The role of topical or systemic prostaglandin inhibitors in cataract surgery has been studied extensively with mixed results. Sanders and Kraff⁵ measured breakdown of the BAB following uncomplicated extracapsular cataract and implant surgery in which patients were given topical indomethacin preoperatively and for two weeks postoperatively. At two weeks fluorophotometry with oral fluorescein was performed and showed reduced BAB breakdown, indicating that indomethacin had an additive or synergistic effect with topical dexamethasone. Pre- and postoperative topical indomethacin in addition to steroids shortened the recovery time of the blood-aqueous barrier from 12 to five weeks but did not influence the integrity of the BAB immediately after surgery.

Miyake¹² performed fluorophotometry (after giving intravenous fluorescein) four weeks after cataract surgery by phacoemulsification and showed less AC fluorescence in those patients treated with topical indomethacin postoperatively, but at two years there was no difference between the treated and placebo groups. Araie *et al*⁸ used fluorophotometry to measure the transfer coefficient of eyes after intracapsular cataract surgery and found that topical indomethacin inhibited barrier disruption at six days after surgery. These results suggest that indomethacin has a beneficial early action but has less influence in the long term. A possible explanation is that the effects of prostaglandin inhibitors are secondary to maintaining pupillary dilatation (which they do very effectively). That is, they may well act by reducing surgical trauma and manipulation to the iris at the time of operation rather than by direct action on the BAB.

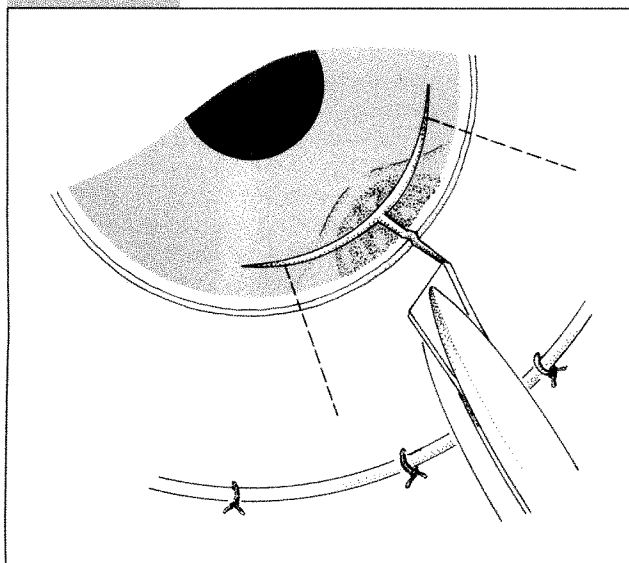
In addition to finding a similar recovery of breakdown of the BAB in all the eyes we have found a uniform rate of return to normality in those eyes that had recovered their BAB by three

months independently of surgeon, type of section, placement of implant, or use of preoperative indomethacin. If fluorophotometry is plotted on a logarithmic scale against time, the rate of recovery can be described by the equation $a=(y-b)/x$, where y is the AC fluorescence and x is the time after surgery. This implies that eyes with higher levels of BAB dysfunction immediately after surgery will recover at the same rate as those with less damage but will take longer to do so, provided this 'normal' recovery process is not interfered with by secondary inflammatory processes. One measurement should be necessary to enable prediction of the duration of recovery of the BAB and to provide a baseline against which changes in surgical technique or postoperative medication could be assessed (Fig 6).

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- 1 Apple DJ, Craythorn JM, Randall JO, *et al.* Anterior segment complications and neovascular glaucoma following implantation of a posterior chamber intraocular lens. *Ophthalmology* 1984; 91: 403-19.
- 2 Sanders DR, Kraff MC, Lieberman HL, Peyman GA, Tarabishy S. Breakdown and reestablishment of blood-aqueous barrier with implant surgery. *Arch Ophthalmol* 1982; 100: 588-90.
- 3 Fearnley IR, Spalton DJ, Smith SE. Anterior segment fluorophotometry in acute anterior uveitis. *Arch Ophthalmol* 1987; 105: 649-56.
- 4 Easty D, Dallas N, O'Malley R. Aphakic macular oedema following prosthetic lens implantation. *Br J Ophthalmol* 1977; 61: 321-6.
- 5 Miyake K, Asakura M, Kobayashi H. Effect of intraocular lens fixation on the blood-aqueous barrier. *Am J Ophthalmol* 1984; 98: 451-5.
- 6 Liesegang TJ, Bourne WM, Brubaker RF. The effect of cataract surgery on the blood-aqueous barrier. *Ophthalmology* 1984; 91: 399-402.
- 7 Sawa M, Sakanishi Y, Okuno Y, Shimizu H. Posterior chamber lens implantation and anterior segment arrier function: a fluorophotometric study. *Jpn J Ophthalmol* 1988; 32: 297-303.
- 8 Araie M, Sawa M, Takase M. Effect of topical indomethacin on the blood-aqueous barrier after intracapsular extraction of senile cataract: a fluorophotometric study. *Jpn J Ophthalmol* 1981; 25: 237-47.
- 9 Menerath JM, Coulangeon LM, Al-Odeh A. Evaluation fluorophotometrique des barrières hématooculaires dans la chirurgie de la cataract. *Ophthalmologie* 1988; 2: 37-40.
- 10 Miyake K, Asakura M, Maekubo K. Consensual reactions of human blood-aqueous barrier to implant operations. *Arch Ophthalmol* 1984; 102: 558-61.
- 11 Champion R, McDonnell PJ, Green WR. Intraocular lenses. Histopathologic characteristics of a large series of autopsy eyes. *Surv Ophthalmol* 1985; 30: 1-32.
- 12 Miyake K. Fluorophotometric evaluation of the blood-ocular barrier function following cataract surgery and intraocular lens implantation. *J Cataract Refract Surg* 1988; 14: 560-8.
- 13 McDonnell PJ, Green WR, Champion R. Pathologic changes in pseudophakia. *Semin Ophthalmol* 1986; 1: 80-103.
- 14 McDonnell PJ, Green WR, Maumenee AE, Iliff WJ. Pathology of intraocular lenses in 33 eyes examined post-mortem. *Ophthalmology* 1983; 90: 386-403.
- 15 Sanders DR, Kraff M. Steroidal and non-steroidal anti-inflammatory agents. Effect on post surgical inflammation and blood-aqueous humor breakdown. *Arch Ophthalmol* 1984; 102: 1453-6.

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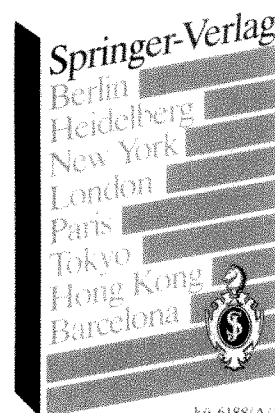
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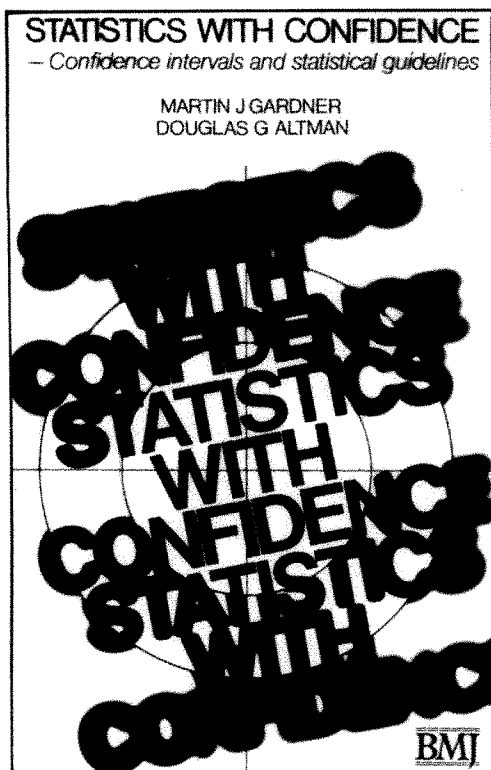


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Table 1 Clinical characteristics: grade of amblyopia and compliance (c)

Grade of amblyopia (VA at start)	Number of cases			
	Anisometropia		Strabismus	
	good c	low c	good c	low c
<0.1	—	—	6	1
0.1-0.3	3	5	15	2
0.4-0.8	9	—	3	—
Total	12	5	24	3

regarded as essential. The same ophthalmologist (JL) and nurse were responsible for the examinations and for giving information to the parents.

Results

The adherence of the 44 children to the amblyopia therapy was graded. Thirty six of the children had good compliance to any form of amblyopic treatment (82%) whereas eight children had low compliance (Table 1).

Of the 36 children with good compliance to any form of treatment 35 were cured according to our definition (one line of acuity difference between the eyes) regardless of type of amblyopia or grade of initial amblyopia in the age group 2 to 7 years. The only 'failure' in this group was a 6-year-old girl with a high degree of anisometropia (retinoscopy right eye +2.5 sph, left eye -6.0 sph -cyl 4.0 ax 0°) combined with a monolateral esotropia. She improved from 0.05 to 0.4 in 90 days, after which no further improvement was possible in spite of optimal compliance. She was the only child who had contact lenses instead of glasses.

The duration of treatment until cure in relation to the age at the start of treatment of compliant children is presented in Figure 2. The treatment time needed to achieve cure for the strabismic children was related to age, with shorter time periods needed on average for the younger

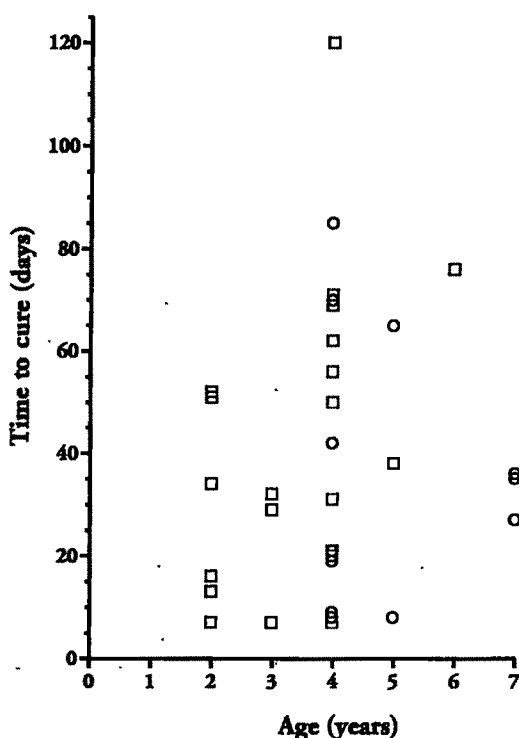


Figure 2 Time to cure (days) vs age (years) for all cured compliant cases with strabismus (n=23) and anisometropia (n=12). Strabismus □. Anisometropia ○.

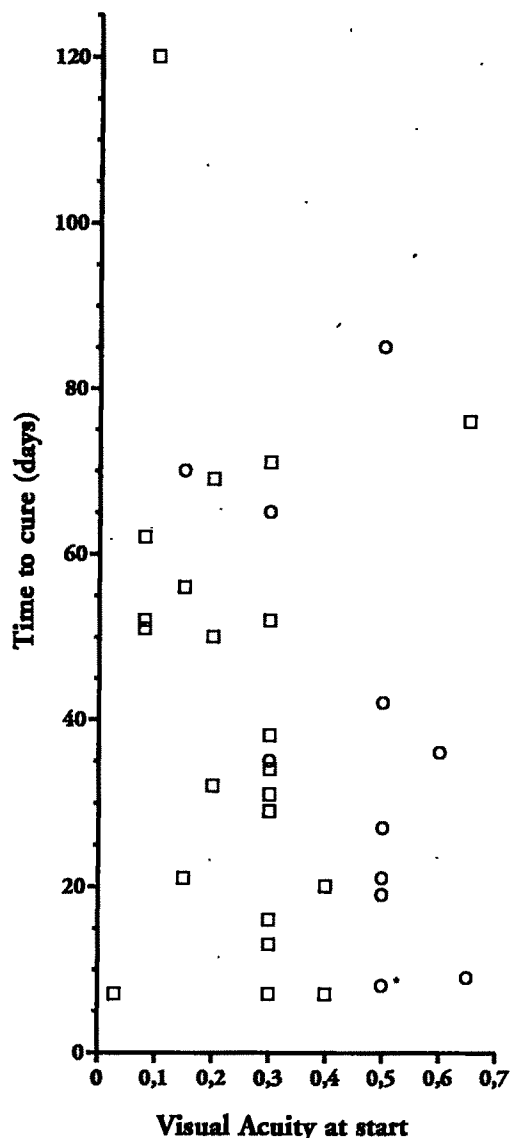


Figure 3 Time to cure (days) vs visual acuity (VA) at start of therapy for all cured compliant children (n=35). *Indicates two identical data points. Strabismus □. Anisometropia ○.

children. For the compliant anisometropes no obvious relation to age was found in the limited age range studied for this group. A more direct comparison between the treatment time needed for strabismic (n=8) or anisometropic (n=7) children aged 4 years, all treated only with repeated patching, revealed that time to cure was in a similar range for both groups in spite of a generally lower VA at the start for the strabismic group. The treatment time until cure ranged from 10 to 80 days for all 4-year-old children compliant to patching. The treatment time to cure for most strabismic and anisometropic cases between 2 and 7 years old with good compliance to any form of amblyopic therapy was 100 days or less (Fig 2). It was not related to initial degree of amblyopia (Fig 3).

Although the treatment regimens other than patching were successful in cases with good compliance, the treatment time to cure, in general, was longer than that for the group with patching. One 7-year-old boy (case 4, outside the time scale in Figs 2 and 3) with microstrabismus (initial VA of 0.2) and treatment with atropine had a treatment time (over 200 days) strikingly longer than the others. However, six children

out of 10 with atropine or Ryser filter treatment were cured within 50 days or less.

To compare the rate of improvement with respect to age and type or grade of amblyopia we evaluated the time needed to improve to the logarithmic half point of VA improvement between start and cure (Figs 4A, B). The time needed to reach this half point was on average shorter at 2 years than at 4 years of age for the strabismic children (Fig 4A). No obvious correlation was found between VA at start of treatment and the time to improve to this half point (Fig 4B). The average improvement during the first weeks of treatment in relation to VA at the start is demonstrated in Fig 5 for three representative groups children, namely those with visual acuity at the start of ≤ 0.1 , 0.3, and 0.5.

Of the total group of 44 children eight showed no or low compliance during the whole or part of the treatment period (Tables 1 and 2). Four of the children in this group were cured in spite of low compliance, but a long treatment period was needed (156 to 412 days). Among the compliant children achieving cure ($n=35$) only one had a treatment time in this time range. Five of the cases with low compliance were anisometropes without strabismus with moderate amblyopia (VA 0.1–0.3) at start of treatment (Table 1). Among all the anisometropic cases with moderate amblyopia at the start the non-compliant children accounted for almost 2/3 (Table 1). The mean age of the children with low compliance was 5.1 years and that of children with good compliance 4.2 years at the start of treatment. However, an age of 2 years (case 18 and 38) was no guarantee of good compliance.

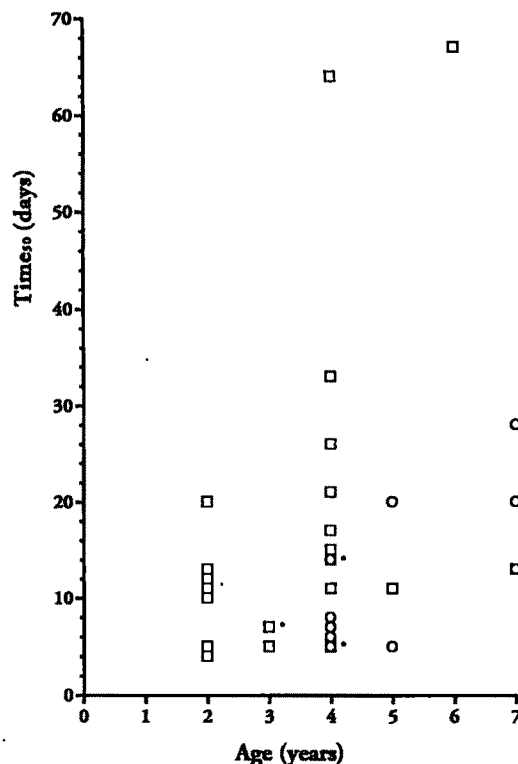


Figure 4A

Occlusion amblyopia was not registered in our 36 compliant children during the treatment period described here, though we observed that three cases on one occasion had one line of poorer performance in the good eye. At the following test the visual acuity returned to normal, though occlusion of the good eye was continued.

Discussion

This prospective study of children with previously untreated amblyopia was initiated in order to delineate limiting factors for cure and to find the reason for failures in different age groups from 2 years and above. A prerequisite for the study of age as a predicting factor for the outcome of amblyopia treatment is tests of acuity suitable for ages from 2 years. In all children below 3 years of age included in this study we could get reliable and reproducible information on visual acuity based on the same general test principle as those used for the older children^{10,13} (Lithander in preparation). The main difference among the optotype tests was the inability to test crowding at the youngest age, since the O test tests acuity for single symbols at near (Lithander, in preparation).

The main question in our study was whether anything could be gained by lowering the age for screening of amblyopia below 4 years. We found no crucial age related differences in the final outcome of treatment, even though the younger age groups showed shorter treatment times. All but one of the compliant children were cured, regardless of age (between 2 and 7 years), diagnosis, and severity of amblyopia. Therefore the present screening program used in Sweden seems adequate. Children with low visual acuity in one or both eyes are detected and referred at the screening age of 4. At any age squint or any other eye disease observed by parents or at the health centre are referred directly to an ophthalmologist for examination and treatment.

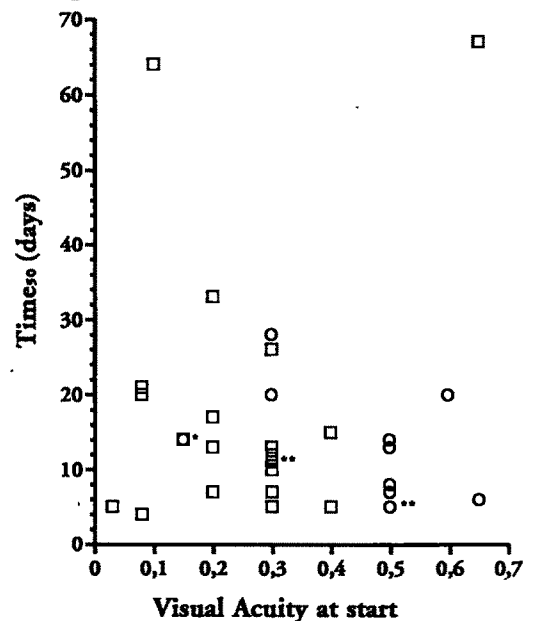


Figure 4B

Figure 4 Initial rate of improvement. Time (days) to halfpoint $\frac{(\log \text{VA start} + \log \text{VA cure})}{2}$ between VA at start and cure for all cured compliant children. (A) Versus age (years) at start of treatment. (B) versus initial degree of amblyopia. *Indicates two identical data points.

Anisometropic and strabismic amblyopia in the age group 2 years and above: a prospective study of the results of treatment

Joan Lithander, Johan Sjöstrand

Abstract

Forty-four children aged 2-9 years with strabismic and anisometropic amblyopia were prospectively followed up during amblyopia treatment. The efficacy of optimised treatment in terms of number of cured children, time to achieve cure, and rate of initial improvement of visual acuity was evaluated in relation to age at start of treatment, type and initial degree of amblyopia, and adherence to treatment regimen. Compliance with treatment was the most critical factor predicting a successful outcome. Among the compliant children 35 out of 36 were cured (visual acuity difference between amblyopic and non-amblyopic eyes not more than one line) within five months regardless of age, treatment regimen, and type or initial degree of amblyopia as compared with none in the group with low compliance. Most of these compliant children were cured within three months, with shorter treatment times on average for the younger children. The initial improvement of visual acuity was also faster at 2 years than at 4 years of age. Anisometropes with moderate amblyopia at the start of treatment were over-represented in the group with low compliance. We conclude that early diagnosis of strabismus in combination with general population screening at the age of 4 to detect amblyopia caused by anisometropia or microstrabismus seems to be efficacious for the cure of most cases. The major factor in treatment failure was found to be inadequate adherence to the treatment regimen.

At 4 years of age the Swedish population is screened for subnormal vision. One major aim is to detect amblyopia by measuring visual acuity at the child health centres. Nordlöw and Joachimsson¹ and Köhler and Stigmar^{2,3} initiated this programme and found it efficacious.

The questions we asked were: Could anything be gained by lowering the screening age? Is earlier treatment more effective and associated with a better outcome? Few systematic studies have evaluated the effect of factors such as age below 4 and type and degree of amblyopia in the treatment of the clinically most common forms of amblyopia, that is, those caused by strabismus or anisometropia.^{4,5}

Most clinicians agree that treatment of amblyopia is less favourable if it appears during the first months of life and if it is associated with extreme degrees of anisometropia.⁶ But the relative importance of various factors for its successful treatment in the more usual clinical

situation is not well defined. The efficacy of screening for the treatment of amblyopia has also been questioned during recent years.⁷⁻⁹

The recent development of accurate methods for testing visual acuity with optotypes in younger children down to an approximate age of 2 years¹⁰ (Lithander, in preparation) has enabled us to study the efficacy of amblyopia treatment as related to optotype acuity over an extended time period. At the same time more interest has been focused on the psychological implications of amblyopia treatment in an active child, and low compliance has been considered to be a major reason for treatment failure in older children.⁵

In this prospective clinical study of children aged 2 years or more we have evaluated the association of various factors such as age at start of treatment and initial degree or type of amblyopia with efficacy of amblyopia treatment. Furthermore, we have analysed factors of importance for the successful outcome of amblyopia therapy.

Patients and methods

PATIENTS

Forty four children aged 2 to 9 years with unilateral amblyopia diagnosed by the first author during the time period 1983-7 at the Paediatric Ophthalmology Unit of Östra Hospital, Göteborg, and fulfilling the inclusion criteria were enrolled consecutively in the study. Inclusion criteria were previously untreated unilateral amblyopia due to strabismus (n=27), or anisometropia without strabismus (n=17), persisting after eight or more weeks of spectacle wear if optical correction was needed. All patients with large angle strabismus, microstrabismus, or strabismus in combination with anisometropia were classified as strabismus. Amblyopia was defined as a difference of at least two lines on the acuity chart between the eyes when tested with best correction after eight weeks with spectacles when needed.

They were mainly referred from the child health centres of Göteborg at any age below 7 years either for squinting problems or for subnormal vision detected at the visual acuity screening test at the age of 4. There were 22 boys and 22 girls. All the children were followed up for at least three years following the start of treatment (mean follow-up time 4.5 years).

CLINICAL EXAMINATION

After retinoscopy optical correction was prescribed when needed for full time use. Aniso-

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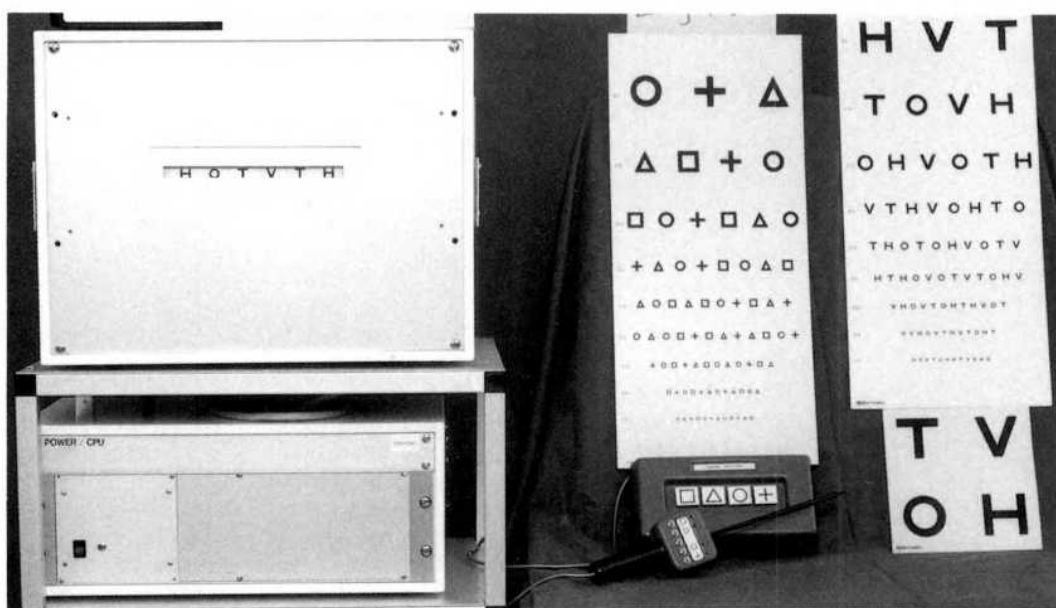


Figure 1 Design principles of the O test, the Kolt test, and HVOT test.

metropia was defined as the difference of one dioptre or more in any symmetrical meridian. The clinical characteristics of the children are summarised in Table 1.

Visual acuity (VA) was assessed at the age 2 to 2½ years with the O-test (Lithander, in preparation). The O-test is a new method designed for testing visual at the age of 18 months and above. It has a testing distance of 40 cm. The child has to point out the O among six symbols, for instance HVTOVH. The O is shown in different positions. It tests visual acuity for single symbols as the interspace between the letters is large. As soon as the child understood the matching symbol principle, the Kolt test with four alternative optotypes (triangle, square, circle, and cross) was used¹⁰ (Lithander, in preparation). The testing distance is 3 m. The children have a matching box with the symbols on four buttons. They have to press the button corresponding to the optotype indicated at the test chart. As reinforcement a melody is played if they perform correctly. The O test, the Kolt test, and the HVOT test are shown in Figure 1. At the age of 4 the HVOT¹ was the elected test. For all the tests above the acuity was tested in approximately logarithmic steps from 0.05 or 0.1 to 1.0. The visual acuity was defined as the line at which ¾ of the optotypes were correctly identified. In cases with VA below 0.1 the testing distance was decreased appropriately and the values transformed.

After the age of 5 visual acuity was tested with Snellen's E chart, and at near Haase's C test with 2.6 arc minutes of interspace between the optotypes.¹² Snellen's letter chart was used, in general, after 7 years of age.

TREATMENT

The primary treatment in all cases was patching on the skin in front of the good eye. The time period for repeated occlusion was selected according to age. Thus a 2-year-old was treated with two days of occlusion and one free day; a 5-year-old child was patched five days and had one

free. Sixteen out of 27 children with strabismus (63%) and 10 out of 17 anisometropes (59%) had no other treatment (except glasses) than patching on the skin until cure. If the child refused or was unable to wear a patch on the skin the second choice of treatment was instillation of atropine in the best eye, if the acuity of the amblyopic eye was above 0.2. In these cases 0.5% atropine was instilled daily for one week followed by one week without treatment, and the treatment cycle was repeated until cure. When the residual amblyopia was mild and problem with the patching occurred, another choice of treatment was a Ryser filter attached to the glass of the good eye.

In order to monitor rate of improvement, time until first cure, and to optimise compliance the children were examined so far as possible every week during the first four weeks and then every second week for the following four weeks. After the start of the third month of follow-up examinations were carried out once a month until cure – that is when one line VA difference or less between the two eyes was achieved. After that, treatment was continued on a part time basis (occlusion of the good eye for one or two hours daily), preferably at children's TV time, until the acuity was equal in both eyes. An exception was in cases of microstrabismus. In this group the endpoint for treatment was one line of acuity difference between the eyes in order to avoid diplopia.

COMPLIANCE

A great effort was made to obtain optimal compliance with treatment. Any problems with either glasses, patching, atropine, Ryser filter, or follow-up were recorded. Low compliance was noted if the prescribed glasses were not worn, if appointments were missed more than once, and if atropine or the Ryser filter was not properly used after a period with problems with patching. Compliance was carefully controlled, as we met the family weekly at the beginning. Detailed information and instructions to the parents and the children before and during treatment were

Table 2 Clinical characteristics of patients (n=8) with low compliance

Case no	Age	Visual acuity		Time to cure (days)
		Start	Cure	
<i>Strabismus</i>				
18	2	0.3	0.5	156
38	2	<0.1	0.5	206
40	9	0.1	0.2*	150*
<i>Anisometropia</i>				
11	4	0.5	0.8	228
39	4	0.3	0.6*	>1000*
42	7	0.2	0.6*	325*
43	6	0.2	0.6*	130*
44	4	0.2	0.8	412

*Cure not achieved; no co-operation obtained for further treatment.

Another major finding in our study was that good compliance to any form of amblyopic treatment was associated with more than 95% cure, whereas only 50% of the children with low compliance were cured. Neumann *et al*⁵ found that a higher proportion of younger children (2–5.5 years) were more compliant to patching than children older than 8 years (72% versus 47%). They concluded that this was probably the primary reason for the higher percentage of treatment failures in older children. Our study shows that low compliance to any form of therapy is also the primary factor for treatment failure in children at any age between 2 and 7 years. The children with low compliance in our study were on average about one year older at start of therapy.

Compliance thus seems to be the main factor for cure, except for those rare cases with therapy-resistant amblyopia, in which amblyopia is probably induced within the first years of life.^{6,14} Emphasis should therefore be placed on adherence to therapy during amblyopia treatment, and initial and repeated information about the importance of compliance to treatment should be given to the family. Follow-up even after a week or two weeks of treatment is rewarding for the visual acuity has improved in most cases (Fig 5), and the child and the parents are hereby encouraged to go on with the treatment. One possible reason for the low improvement rate of severe amblyopia found in some studies⁸ could be low compliance.

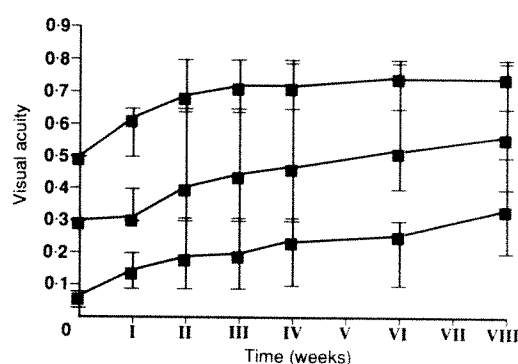


Figure 5 Rate of improvement during the first weeks of amblyopia treatment in relation to visual acuity of the amblyopic eye at start. The range of VA at one to eight weeks after start is presented for three representative groups of cured compliant children with initial VA of ≤ 0.1 (n=5), 0.3 (n=10), and 0.5 (n=5). The ranges overlap for the two groups, with higher initial VA between four and eight weeks as indicated and for the group with initial VA ≤ 0.1 at eight weeks. Identical range limits are indicated by double horizontal bars.

Although we put much time and effort into information we had eight out of 44 with low or no compliance. Five of these children had moderate amblyopia – that is, visual acuity 0.1 to 0.3 due to anisometropia without strabismus. In the anisometropic group with mild amblyopia – that is, visual acuity above 0.4 – we had no problems with compliance. Neumann *et al*¹⁵ also reported the lowest rate of compliance in the group with anisometropic amblyopia.

The question arises why it is so difficult for the anisometropic child with visual acuity of 0.1–0.3 to accept a patch. A probable answer is that lower degree of motivation for treatment was present for patients in this group with straight eyes. Our five anisometropic children with low compliance were treated for long periods (years), and periods of adequate compliance were obtained. All of them had improvement of at least three lines and two were finally cured, so their amblyopia is probably not resistant to therapy. However, our study cannot rule out the possibility that the therapeutic responses in anisometropia and strabismic amblyopia are different. It is interesting to note that the two types of amblyopia have differences in psychophysical characteristics.^{16–18}

The treatment time needed to achieve cure, namely one line difference or less between the eyes, was highly dependent on compliance but not on the initial type or degree of amblyopia. All but two of the compliant children were cured within three months of treatment regardless of initial visual acuity or type of amblyopia in contrast to the children with lower compliance. Treatment regimen and type of amblyopia therefore seems to have limited impact on the time needed to achieve cure. Similarly, Oliver *et al*⁵ and Neumann *et al*¹⁵ reported that most of the improvement of visual acuity occurred during the first three months of treatment independently of type or initial degree of amblyopia. The rate of initial improvement in our compliant children showed no obvious correlation with visual acuity at the start of treatment, though a tendency may be observed. Neumann *et al*¹⁵ have reported a quicker recovery of visual acuity after three months of treatment in children (aged 2–7 years) with more severe amblyopia at the start.

Our study hypothesis that age is a strong factor in the outcome of amblyopia treatment was not supported. Instead we found that the age of the child was not critical for a successful result. However, the number of children above 5 years of age in our study was limited. Age was only weakly associated with the time needed to achieve cure in the age group 2–7 years in cases with good compliance. Similarly, Oliver and Nawratzki¹ found that up to the age of 6 years good therapeutic results (about 65%) were obtained in all age groups. They stated that most children with amblyopia can be effectively detected at the age of 4 years and concluded that this age probably is the best age for screening, also taking into account that the prevalence of amblyopia is lower below 3 years of age.¹ At 2 years of age our strabismic children were cured somewhat quicker than the older ones, but this difference in cure rate is of limited practical importance if we consider the lower accuracy of acuity testing under screening conditions at earlier ages. Fulton

and Mayer¹⁹ reported similar results in a retrospective study of the relationship between age and duration of full-time occlusion in squinting children and demonstrated that older children show a slower rate of acuity improvement during patching. Sattler²⁰ found a quick recovery within the first three months of treatment for 3-year-old children with squint than for those aged 7 or above.

Flynn and Cassady²¹ demonstrated a decreasing percentage of successful results and prolonged duration of therapy in amblyopic children with start of therapy after 5 years of age. Screening after the age of 6 is therefore probably suboptimal from the therapeutic point of view.

In summary, in our study, designed to be optimal for amblyopia treatment, we found that the patient's compliance was the main factor in achieving cure in most cases with strabismus and anisometropia in children between 2 and 7 years. Most of the improvement occurred during the first months and the majority (>90%) were cured within three months irrespective of age between 2 and 7 years. Visual acuity screening at 4 years of age seems to be advantageous and efficacious in order to detect and thereafter initiate successful treatment of most cases of amblyopia without obvious squint.

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We thank Maths Abrahamsson for help with the illustrations and for useful discussions and Lena Kjellberg for skilful assistance.

- 1 Nordlöw W, Joschimsson S. A screening test for visual acuity in four-year-old children. *Acta Ophthalmol (Kbh)* 1962; 40: 453-62.
- 2 Köhler L, Stigmar G. Vision screening of four-year-old children. *Acta Paediatr Scand* 1973; 62: 17-27.
- 3 Köhler L, Stigmar G. Visual disorders in 7-year-old children with and without previous vision screening. *Acta Paediatr Scand* 1978; 67: 373-7.
- 4 Oliver M, Nawratzki I. Screening of pre-school children for ocular anomalies. II. Amblyopia. Prevalence and therapeutic results at different ages. *Br J Ophthalmol* 1971; 55: 467-71.
- 5 Oliver M, Neumann R, Chaimovitch Y, Gottesman N, Shimshoni M. Compliance and results of treatment for amblyopia in children more than 8 years old. *Am J Ophthalmol* 1986; 102: 340-5.
- 6 von Noorden GK. Amblyopia: a multidisciplinary approach. *Invest Ophthalmol Vis Sci* 1985; 26: 1704-15.
- 7 Stewart-Brown SL, Haslum MN, Howlett B. Preschool vision screening: a service in need of rationalisation. *Arch Dis Child* 1988; 63: 356-9.
- 8 Ingram RM. Review of children referred from the school vision screening programme in Kettering during 1976-8. *Br Med J* 1989; 298: 935-6.
- 9 Ingram RM, Walker C, Billingham B, Lucas J, Dally S. Factors relating to visual acuity in children who have been treated for convergent squint. *Br J Ophthalmol* 1990; 74: 82-3.
- 10 Lithander J. Kolt-Test Prüfung der Sehschärfe bei 2-jährigen. *Z Prakt Augenheilkd* 1984; 5: 258.
- 11 Hedin A, Nyman KG, Derouet B. A modified letter matching chart for testing young children's visual acuity. *J Pediatr Ophthalmol Strabismus* 1980; 17: 114-8.
- 12 Haase W, Hohmann A. Ein neuer Test (C Test) zur quantitativen Prüfung der Trennschwierigkeiten (crowding) - Ergebnisse bei Amblyopi und Ametropi. *Klin Monatsbl Augenheilkd* 1988; 180: 210-5.
- 13 Cavazos H, Schulz E, Rassow B, Weseman W. Vergleich des Kinderscharfetestes nach Lithander (Kolt-Test) mit dem standardisiertem Landoltring. *Klin Monatsbl Augenheilkd* in press.
- 14 Parks MM. Visual results in aphakic children. *Am J Ophthalmol* 1982; 94: 441-9.
- 15 Neumann R, Oliver M, Gottesmann N, Shimshoni M. Prognosis for occlusive therapy for strabismic and anisometropic amblyopia and for different initial depths of amblyopia. *Chibrai Int J Ophthalmol* 1989; 6: 22-7.
- 16 Levi DM, Klein S. Differences in vernier discriminations for gratings between strabismic and anisometropic amblyopes. *Invest Ophthalmol Vis Sci* 1982; 23: 398-407.
- 17 Hess RF, Campbell FW, Zimmern R. Differences in the neural basis of human amblyopias: the effect of mean luminance. *Vision Res* 1980; 20: 295-305.
- 18 Sjöstrand J. Contrast sensitivity in children with strabismic and anisometropic amblyopia. A study of the effect of treatment. *Acta Ophthalmol (Kbh)* 1981; 59: 25-33.
- 19 Fulton AB, Mayer DL. Esotropic children with amblyopia: effects of patching on acuity. *Graefes Arch Clin Exp Ophthalmol* 1988; 226: 309-12.
- 20 Sattler CH. Erfahrungen über die Beseitigung der Amblyopie und die Wiederherstellung des binokularen Sehakts bei Schielenden. *Z Augenheilkd* 1927; 63: 19-37.
- 21 Flynn JT, Cassady JC. Current trends in amblyopia therapy. *Ophthalmology* 1978; 85: 428-50.

Corneal sensitivity and correlations between decreased sensitivity and anterior segment pathology in ocular leprosy

Murat A Karaçorlu, Tülay Çakiner, Türkan Saylan

Abstract

Leprosy is one of the leading causes of corneal hyposensitivity. In this article the corneal sensitivity of 143 leprosy patients was examined, and correlations between corneal hyposensitivity and anterior segment pathology were detected. Twenty four healthy volunteers were examined as controls. Various degrees of corneal loss of sensitivity were found in 46.2% of leprosy patients. Lagophthalmos, chronic lepromatous granulomatous uveitis, iris atrophy, and social blindness were found 4.5-16.6 times more frequently in eyes which developed severe corneal hyposensitivity.

Leprosy, the agent of which is *Mycobacterium leprae*, is one of the systemic and infectious diseases which mostly involve the eye.¹⁻³ Regardless of the portal of entry of the leprosy bacillus the target tissue is the Schwann cells of peripheral nerves.⁴ The bacillus prefers the nerves in areas where the body temperature is low. It may affect the zygomatic branch of nervus facialis and corneal nerves innervated by the ophthalmic branch of the trigeminal nerve.⁵

Although it has long been known that in leprosy corneal sensitivity is decreased, the degree of hyposensitivity, how frequently it appears, whether or not it leads to anaesthesia, and whether it is correlated with anterior segment lesions of leprosy have not been completely evaluated. Various rates of corneal hyposensitivity have been reported, but few of these studies are quantitative, carried out with cotton, and control groups have generally not been included.

In this study we have investigated the actual incidence of corneal hyposensitivity in leprosy and tried to answer those questions.

Materials and methods

The study was carried out in the Department of Ophthalmology, Cerrahpaşa School of Medicine, University of Istanbul, and Istanbul Leprosy Hospital and Research Centre, from June 1986 through June 1989. A total of 286 eyes were included, from 88 patients with lepromatous leprosy (LL) and 55 patients with borderline lepromatous leprosy (BL). As controls, 48 eyes of 24 healthy adults who had no ocular or systemic diseases and who were not taking any topical or systemic medication when they were included in the study. The study was carried out prospectively, and all ophthalmic examinations and corneal sensitivity measurements were made by the same researcher (MAK). Since there were

visible deformities in some of the patients, masking of the investigator was of no use.

The diagnosis of leprosy was established by the case history, clinical and bacteriological tests, and in some cases histopathological investigations at Istanbul Leprosy Hospital and Research Centre. The patients were sent to our working group for ophthalmic evaluation, regardless of whether or not they had any complaints. The cases were classified by the Ridley-Jopling classification.⁶

Systemic and ophthalmic examinations of all patients were undertaken and were recorded on previously prepared forms. Corneal sensitivity was measured by the Cochet-Bonnet aesthesiometer and the intraocular pressure by the Goldmann applanation tonometer.

MEASUREMENT OF CORNEAL SENSITIVITY

Before the corneal sensitivity measurement was carried out the reason for it and the method were explained to the patient, and his co-operation was sought. The patient, sitting before the biomicroscope, was fixated on an asterisk placed in the distance, lest he should see the filament by means of accommodation. The examination was initiated by a filament 60 mm in length. The cornea, divided into four quadrants and one central area, was measured first at the centre, and the measurements were then continued clockwise beginning from the lower nasal quadrant. The blinking reflex was not accepted as a response to the contact of the filament. The patient was asked if he felt the contact of the filament, and sometimes the accuracy of his answer was verified by approaching the filament to the cornea but not touching it and asking the patient the same question. The examination began with 60 mm of filament and was continued by shortening the filament by 5 mm, until the patient responded that he did not feel the contact of the filament. Measurements were carried out in the afternoon from 1300 to 1700 with the same aesthesiometer, in the same setting, and by the same researcher, but the temperature and humidity control of the examination room was not verified.

SEVERITY OF CORNEAL HYPOSENSITIVITY

The severity of corneal hyposensitivity was graded in the groups included in the study. Those who had a mean corneal sensitivity of 55 mm or more, measured in five separate quadrants of the cornea, were considered to have normal corneal sensitivity. Corneas having a value of 50-54 mm were considered as showing a

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Table 1 Corneal sensitivity values in the eyes of leprosy patients and the normal control group in relation to the quadrants of the cornea

Corneal quadrants	Leprosy eyes n:286	Control group n:48	p
Centre	52.5 (11.8)*	57.2 (4.3)	0.007
Upper temporal	48.0 (14.1)	54.0 (6.3)	0.004
Upper nasal	46.5 (14.2)	54.5 (5.4)	0.001
Lower nasal	52.3 (11.2)	57.6 (4.6)	0.002
Lower temporal	52.4 (12.3)	57.5 (4.7)	0.005
Average	50.3 (12.1)	56.2 (4.3)	0.001

*Millimetres, mean (SD).

slight hyposensitivity, those with a value of 40–49 mm had a moderate hyposensitivity, and those with a value of 30–39 mm had a severe hyposensitivity. The patients with a value of 30 mm or lower were considered to have an advanced degree of corneal hyposensitivity.

Student's *t* test and analysis of variance were used for statistical analysis.

Results

The mean age (with SD) of the patients with lepromatous leprosy was 42.0 (13.7) years, those with borderline lepromatous leprosy 40.8 (13.0) years, and of the control group 40.7 (12.7) years. The duration of the disease was 20.6 (12.7) years in cases with LL and 18.1 (11.3) years in those with BL.

When the measurements of corneal sensitivity by quadrants of the leprosy patients and of the normal control group were compared, the sensitivity in all the quadrants of the leprosy patients was significantly low, being lowest in the upper nasal quadrant (Table 1).

When the cases of LL and BL were studied separately, corneal sensitivity in all quadrants was found to be significantly lower in the group with lepromatous leprosy than in the control group. In cases with borderline lepromatous leprosy, though the mean corneal sensitivity was lower than in the control group, the decrease was statistically significant only for the upper nasal quadrant (Table 2).

When the correlation between the duration of the disease and corneal hyposensitivity was investigated in the patients with LL and BL leprosy, it was observed that corneal sensitivity was significantly lower in cases with a duration over 15 years as compared with the control group (Table 3).

When the severity of corneal hyposensitivity was evaluated, the proportion of cases in which

Table 2 Corneal sensitivity values in LL, BL, and control groups in relation to the quadrants of the cornea

Corneal quadrants	LL n:176	BL n:110	Control group n:48
Centre	50.0 (13.7)*	56.5 (6.2)	57.2 (4.3)
p	<0.001	>0.05	
Upper temporal	45.2 (15.9)	52.6 (8.9)	54.0 (6.3)
p	<0.001	>0.05	
Upper nasal	43.6 (15.8)	51.0 (9.8)	54.5 (5.4)
p	<0.001	<0.05	
Lower nasal	50.0 (13.4)	56.0 (6.6)	57.6 (4.6)
p	<0.001	>0.05	
Lower temporal	49.8 (14.3)	56.6 (6.1)	57.5 (4.7)
p	<0.001	>0.05	
Average	47.7 (13.9)	54.5 (6.6)	56.2 (4.3)
p	<0.001	>0.05	

*Millimetres, mean (SD).

Table 3 Correlation between the duration of disease and corneal hyposensitivity in leprosy patients

Duration of disease (yr)	n (%)	LL+BL eyes n:286	Control group n:48	p
0–5	36 (% 12.6)	53.5 (9.1)*	56.2 (4.3)	>0.05
6–10	56 (% 19.6)	56.3 (6.2)	56.2 (4.3)	>0.05
11–15	28 (% 9.8)	51.2 (12.6)	56.2 (4.3)	>0.05
16–20	48 (% 16.8)	49.8 (13.5)	56.2 (4.3)	<0.01
>20	118 (% 41.2)	46.4 (12.9)	56.2 (4.3)	<0.003

*Average values, millimetres, mean (SD).

the sensitivity of all five corneal quadrants was 55 mm or more in the control group was 72.9%. This rate was 53.8% in patients with leprosy. While the value of corneal sensitivity was below 50 mm in 6.3% of patients in the control group, it was 32.2% in patients with leprosy (Table 4). Table 4 shows that, in 46.2% of patients with leprosy, there were various degrees of corneal hyposensitivity.

In order to investigate the correlation of corneal hyposensitivity with the anterior segment pathology in leprosy, a group of patients with leprosy who had normal corneal sensitivity (154) were compared with another group of patients with leprosy (30) who had an advanced degree of hyposensitivity responding only to the filament length below 30 mm (4th degree), and the incidence of anterior segment pathology was investigated in both groups (Table 5).

Discussion

In leprosy the organ most often involved after the skin, nasal mucosa, and peripheral nerves is the eye. The eye is liable to infiltration as soon as the disease agent disseminates through the blood stream. The leprosy bacillus may be present in any part of the eye, but the main lesion is almost always in the structures of anterior segment. Although the primary lesions appear on the cornea, it has been suggested that the earliest affected part is the ciliary body.³⁷

The involvement of the trigeminal nerve-ends in the cornea, together with the zygomatic branch of the facial nerve, leads on to the association of corneal hyposensitivity with lagophthalmos, and this in turn indicates how liable the globe has been to the risks inherent in leprosy.

The incidence of corneal hyposensitivity in leprosy has been reported as being between 8.1% and 59.2%. As noted above, most of these studies lack valid scientific criteria. Table 6 shows the incidence of corneal hyposensitivity reported in literature.

When the results of our study are examined, it is seen that corneal hyposensitivity in cases with lepromatous leprosy, although the duration of the disease is not different, is more severe than in

Table 4 Severity of corneal hyposensitivity in patients with leprosy and the control group

Severity of corneal hyposensitivity	Leprosy eyes n:286	Control group n:48
Normal (50–60 mm)	154 (% 53.8)	35 (% 72.9)
1st degree (mild) (50–54 mm)	40 (% 14.0)	10 (% 20.8)
2nd degree (moderate) (40–49 mm)	46 (% 16.1)	3 (% 6.3)
3rd degree (severe) (30–39 mm)	16 (% 5.6)	–
4th degree (advanced) (<30 mm)	30 (% 10.5)	–

Table 5 Incidence of anterior segment lesions in leprosy patients with normal corneal sensitivity and leprosy patients with advanced degree of corneal hyposensitivity (4th degree)

Anterior segment lesions related to leprosy	Normal sensitivity 154 (% 53.8)* %	Advanced hyposensitivity 30 (% 10.5) %
Prominent corneal nerves	32.5	23.3
Corneal nerve beading	33.8	20.0
Avascular keratitis	15.6	3.3
Exposure keratitis	3.9	46.7
Acute non-granulomatous uveitis	13.0	6.7
Chronic granulomatous uveitis	20.1	96.7
Iris atrophy	17.5	80.0
Social blindness (<3/60)	0.6	10.0

*The number among leprosy patients.

Table 6 Incidence of corneal hyposensitivity in leprosy according to various studies

Authors	Year	%
Shields <i>et al</i> ⁸	1971	36
Acharya ⁹	1978	59.2
Courtright <i>et al</i> ¹⁰	1984	20
Prasad <i>et al</i> ¹¹	1984	8.1
Ffytch ¹²	1984	20
Tsai and Suryawanshi ¹³	1985	24
Present study	1989	46.2

cases of borderline lepromatous leprosy and that, the longer the duration of the disease, the worse is the hyposensitivity.

When the topographical distribution of corneal hyposensitivity is examined, the most severe hyposensitivity is found in the upper nasal and temporal quadrants, whether in cases of lepromatous leprosy or of borderline lepromatous leprosy, and that, although there is some hyposensitivity in the corneal centre, this has been relatively less than in the outer quadrants.

Corneal hyposensitivity was examined in the normal state and in four degrees of severity, and it was found that the patients with advanced hyposensitivity who responded to a filament length of less than 30 mm had had the disease for significantly longer than the leprosy patients with normal corneal sensitivity, and that they became leprous when they were considerably younger.

Various rates of hyposensitivity were determined in 46.2% of leprous patients. Even when the confidence limit was assumed to be 95%, this rate showed such a high value as 32.2% approximately.

Contrary to mistaken beliefs, leprosy was not found to cause deep corneal hyposensitivity approaching anaesthesia. In this study the number of eyes which had a mean corneal hyposensitivity under 5 mm was 0.6%. The

percentage of such cases has been reported to be 53.3% in patients with herpetic stromal keratitis.¹⁴ Leprosy causes less corneal hyposensitivity than herpetic stromal keratitis.

When the leprosy patients with no corneal hyposensitivity and those with advanced corneal hyposensitivity were divided into two groups and examined as to the leprous lesions in the anterior segment, it was found that, in the first group, avascular keratitis occurred approximately five times and acute non-granulomatous uveitis twice as frequently; whereas in the second group, that is, in the cases with advanced hyposensitivity, chronic granulomatous lepromatous uveitis occurred approximately five times, iris atrophy four times, and social blindness 16 times as frequently.

It has been shown that leprosy causes a high percentage of corneal hyposensitivity among patients with the disease in Turkey, and that severe corneal hyposensitivity was more frequent among cases of lepromatous leprosy. The incidence increased with duration of disease, and in patients with advanced corneal hyposensitivity the anterior segment lesions of this disease were found more often.

1 Brand ME, Ffytche TJ. Eye complications of leprosy. In: Hastings RC, ed. *Leprosy*. Edinburgh, London: Churchill-Livingstone, 1985: 223-42.

2 Rees RJW. The microbiology of leprosy. In: Hastings RC, ed. *Leprosy*. Edinburgh, London: Churchill-Livingstone, 1985: 31-2.

3 Karaçorlu M, Çakiner T. Lepira hastalığında göz problemleri. In: Saylan T, Süttaş M, eds. *II. Ulusal Lepira Smineri*. İstanbul: Yaylacık Matbaası, 1986: 99-107.

4 Ridley DS. Lepirada histolojinin uygulanması, tanı, sınıflandırma ve reaksiyonlar. In: Saylan T, Süttaş M, eds. *II. Ulusal Lepira Smineri*. İstanbul: Yaylacık Matbaası, 1986: 79-89.

5 Ridley MJ. Lepiranin mikrobiyolojisi. In: Saylan T, Süttaş M, eds. *II. Ulusal Lepira Smineri*. İstanbul: Yaylacık Matbaası, 1986: 65-71.

6 Ridley DS, Jopling WH. Classification of leprosy according to immunity: a five-group system. *Int J Lepr Other Mycobact Dis* 1966; 34: 255-73.

7 Brand MB. *Care of the eye in Hansen disease*. 2nd ed. Carville, LA: Star, 1987: 3-14.

8 Shields JA, Waring III GO, Monte LG. Ocular findings in leprosy. *Am J Ophthalmol* 1974; 77: 880-90.

9 Acharya BP. Ocular involvement in leprosy (a study in mining areas of India). *Ind J Ophthalmol* 1978; 11: 21-4.

10 Courtright P, Green R, Pilorski R, Smuony J. A survey of the eye complications of leprosy in South Korea. *Lepr Rev* 1984; 55: 229-37.

11 Prasad VN, Norain M, Mukhiya RD, Bist HK, Khan MM. A study of ocular complications of leprosy. *Indian J Lepr* 1984; 56: 241-50.

12 Ffytche TJ. The American Peace Corps survey of the ocular complications of leprosy in South Korea, an evaluation and appraisal. *Lepr Rev* 1984; 55: 239-46.

13 Tsai HH, Suryawanshi N. Ocular complications in patients with leprosy in Karigiri, South India. *Lepr Rev* 1985; 56: 135-41.

14 Karaçorlu M, Özyazgan Y, Erçikan C. Herpes simpleks virüsü (HSV) aktif stromal keratitli olgularda klinik özellikler ve kornea duyu değişimleri. *Türk Oft Gaz* (in press).

Influence of untreated chronic plastic iridocyclitis on intraocular pressure in leprosy patients

Murat A Karaçorlu, Tülay Çakiner, Türkan Saylan

Abstract

The intraocular pressures of a total of 286 eyes of patients with lepromatous and borderline lepromatous leprosy who never had regular ophthalmological care or local eye treatment were measured. The patients were categorised according to the type of leprosy they had, and the eyes were categorised as without or with chronic plastic iridocyclitis. In patients with lepromatous and borderline lepromatous types of leprosy the intraocular pressure was significantly lower in eyes with chronic plastic iridocyclitis 10.1 (3.6) mmHg than in both unaffected eyes 11.0 (3.2) mmHg and control eyes 13.5 (2.5) mmHg. It has been shown that chronic plastic iridocyclitis which remains untreated for years results in a lower intraocular pressure than normal.

In leprosy patients chronic plastic iridocyclitis (CPI) affects ocular physiology gradually and as a consequence may lead to lesions causing complicated cataract and phthisis bulb.^{1,2} There has been only one study questioning the effect of CPI on intraocular pressure (IOP) in leprosy.³ In this study the Schiøtz tonometer was used, and, since the study was carried out in rural areas in Nepal, a biomicroscope was not available and only synechiae were used as the diagnostic criteria of CPI. It is difficult to make accurate measurements under conditions of very low pressures with the Schiøtz tonometer. Moreover, in the above mentioned study the diagnosis of CPI was based on insufficient criteria. For these reasons the accuracy of the results may be questioned.

The low prevalence of leprosy in Turkey and its being not well known has caused delay in establishing the diagnosis and beginning treatment.⁴ This delay has been presumed to be 5-10 years (personal communication, Saylan T, 1986). We know that in leprosy the first symptoms of ocular involvement appear approximately five years after the onset of the disease, and therefore a number of patients in our country have attacks of leprosy uveitis of short or long duration before diagnosis of leprosy has been established. If it is remembered that chronic leprosy uveitis is not a cause of much complaint, we may realise what kind of risks these patients run. Apart from this

one cannot claim that complete and regular leprosy therapy was carried out in our country before 1983. Only after that year was regular, modern leprosy therapy with a variety of drugs started. If we consider that the mean duration of disease has been about 20 years in the lepromatous leprosy (LL) and borderline leprosy (BL) patients we have been following up, we may conclude that in some of our patients the disease has been undiagnosed and without treatment for a long time.

In this study, because of the above mentioned reasons, the IOPs of our leprosy patients who have long been left untreated have been measured by applanation tonometer in a prospective but non-random and unmasked study, and the effect of CPI on the IOP has been investigated.

Materials and methods

The study was carried out from June 1986 to the end of 1989 by the Department of Ophthalmology, Cerrahpaşa School of Medicine, University of Istanbul, and Istanbul Leprosy Hospital and Research Centre. It included 286 eyes of 143 leprosy patients, 88 of whom had lepromatous leprosy (LL) and 55 borderline lepromatous leprosy (BL). As the control group, 48 eyes of 24 adults were taken, matched by age to the study group, who had not had any ocular or systemic diseases, and who were not receiving topical or systemic medication.

The type of leprosy was diagnosed according to the Ridley-Jopling⁵ classification of clinical, microbiological and histological criteria in the Istanbul Leprosy Hospital. The diagnosis of chronic plastic iridocyclitis was established when keratic precipitates, posterior synechiae, sequelae of posterior synechiae, iris atrophy, or iris pearl were detected.

The systemic leprosy treatment of 76 of the cases (53.1%) was terminated before they were included in the study. Sixty seven of them (46.9%) received multidrug leprosy treatment - DDS (dapsone or disulone)+rifampicin+prothionamid (promid), or alternatively clofazimine (lamprone) - when they were included in the study.

The mean age of the control group was 40.7 (12.3) years, and that of leprosy patients (LL+BL) 41.5 (13.4) years. The mean duration of the disease in patients with leprosy was 19.7 (12.2) years. The ages and the duration of the disease of the patients with LL and BL are shown in Table 1.

The ophthalmic examination of the leprosy patients included examination of the anterior segment by biomicroscope. Their IOPs were measured by Goldmann applanation tonometer. The findings have been recorded on a form.

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Table 1 Ages and duration of the disease of the patients with lepromatous leprosy (LL) and borderline lepromatous leprosy (BL)

	Age (yr)			Total	Disease duration (yr)			Total
	<20	20-40	>40		<10	10-20	>20	
Lepromatous Leprosy (LL)	8	78	90	176	58	40	78	176
Borderline Lepromatous	4.5%	44.4%	51.1%		33%	22.7%	44.3%	
Leprosy (BL)	4	50	56	110	34	36	40	110
	3.6%	45.4%	50.9%		30.9%	32.8%	36.3%	

Table 2 Distribution of the intraocular pressure in 286 eyes of patients with lepromatous leprosy and borderline lepromatous leprosy

	Intraocular pressure mmHg										Mean (SD) IOP (mmHg)
	3-5	6-7	8-9	10-11	12-13	14-15	16-17	18-19	20-21	≥22	
CPI (+) n=118	7 (5.9)*	16 (13.6)	35 (29.7)	28 (23.7)	17 (14.4)	9 (7.6)	2 (1.6)	1 (0.8)	1 (0.8)	2 (1.6)	10.1 (3.6)
CPI (-) n=168	5 (3.0)	18 (10.7)	28 (16.7)	49 (23.9)	32 (13.8)	22 (12.9)	6 (3.5)	4 (2.3)	4 (2.3)	-	11.0 (3.3)
Total n=286	12 (4.2)	34 (11.9)	63 (22.0)	77 (26.9)	49 (17.1)	31 (10.8)	8 (2.8)	5 (1.8)	5 (1.8)	2 (0.7)	10.6 (3.5)

*The figures in brackets show the percentage values.

Results

The distribution of the IOP in patients with leprosy who had or had not established findings of CPI are shown in Table 2.

The mean (SD) IOP was 10.1 (3.6) mmHg in leprosy patients with CPI, and 11.0 (3.3) mmHg in those without established CPI. The mean IOP of the control group was 13.5 (2.5) mmHg. The mean IOP of leprosy cases with established CPI findings was significantly lower than the IOP in either the cases without established CPI or of the control group ($p<0.05$) and ($p<0.001$). Moreover, the difference between the eyes without CPI and the control group was significant ($p<0.05$).

When the relation between the duration of leprosy and IOP was investigated, the mean IOP was found to become lower as the duration of the disease was longer. The mean IOP of patients who had had leprosy for more than 15 years was significantly lower than in patients with leprosy for 0-5 years ($p<0.005-0.001$) (Table 3).

When the distribution of the lower IOPs was investigated the IOP was below 10 mmHg in seven eyes (14.5%) in the healthy control group, whereas this proportion increased to 109 (38.1%) in all the leprosy patients. When only the eyes with established CPI were included 58 patients (49.2%) out of 118 with CPI were found to have an IOP below 10 mmHg. In 51 (30.4%) out of 168 eyes with negative CPI the IOP was found to be below 10 mmHg (Tables 4 and 5).

Discussion

Leprosy affects the eye by multiplication of leprosy bacilli and by spreading through the body via the blood stream in patients with a deficient cellular immune response. The bacillus may be present in any part of the eye, but the lesions it causes are almost always localised in the anterior segment. It is presumed that the earliest affected part of the eye is the ciliary body. Bacteria pass from there to the surrounding tissues by way of the blood stream, nerves, and adjacent tissues.^{1,2}

Especially in patients with LL and BL,

'erythema nodosum leprosum' (or type II reaction, another name for it), which is a systemic immune complex disease, may develop by the antigenic effect of the leprosy bacilli. During this event the testicles, joints, and kidneys become involved together with the eyes.⁶ Acute non-granulomatous iridocyclitis develops in the eye. Moreover, chronic granulomatous lepromatous iritis also develops after the invasion of the leprosy bacillus.^{1,2}

It has been presumed that these recurrent uveitis attacks, which have an insidious and continuous course, affect the secretory epithelium in the ciliary body and prevent its proper functioning. There have been reports which demonstrate the frequency of these recurrent iridocyclitis attacks and the disturbance of the dynamics in aqueous humour.^{7,8}

Histopathological studies carried out in the iris and ciliary body of the eyes involved in iridocyclitis have demonstrated epithelial damage, widespread mononuclear cell infiltration in the stroma, hyalinisation, fibrosis, and atrophy.⁷ In another study it has been reported that in patients with Behçet's disease the c value has been lowered to pathological levels in the eyes with more than five attacks, and that secondary glaucoma appeared in only a small number of these eyes; the reason for this has maybe the decrease in the secretory rate.⁸ Slem has also reported that production of aqueous humour is significantly lowered in patients with leprosy.⁹

Brandt *et al*³ reported that they found CPI in 22.3% of cases with lepromatous leprosy, and suggested that the IOP is lower in the eyes with CPI than in eyes without it.

In our study we found CPI in 41.2% of cases of leprosy, and the mean IOP in these cases was

Table 4 The distribution of lower IOP values in leprosy patients in control group

IOP mmHg	Leprosy Patients n=268	Control group n=48
≤5	12 (4.2)*	-
6-7	34 (11.9)	-
8-9	63 (22.0)	7 (14.5)
≥10	177 (61.9)	41 (85.5)

Percentages in brackets

Table 5 The distribution of lower IOP values (<10 mmHg) in leprosy patients with and without CPI, and control group

	IOP <10 mmHg	
	n	%
CPI (+) leprosy eyes n=118	58	49.2
CPI (-) leprosy eyes n=168	51	30.4
Normal control group n=48	7	14.5

Table 3 The relation between the duration of leprosy and intraocular pressure (IOP)

Duration of disease	Age (yr) mean (SD)	n	IOP mmHg mean (SD)	p
0-5	33.5 (18.1)	36	12.3 (4.6)	-
6-10	32.5 (8.6)	56	11.1 (4.0)	>0.05
11-15	39.2 (12.6)	28	11.0 (1.9)	>0.05
16-20	39.1 (11.3)	48	9.5 (2.1)	<0.001
>20	49.8 (9.3)	118	10.3 (3.3)	<0.005

significantly lower than in the control group or in patients with CPI. There was a statistically significant difference between the IOP in patients with leprosy but without CPI and the control group. We have assumed that there are two reasons for this condition. The first is that, since iridocyclitis does not always cause persistent lesions, these eyes have in fact, had iridocyclitis attacks but without sequelae. Further, we presume that the bacillus has involved the autonomic nervous system¹⁰ and has affected neurogenous mechanisms of the aqueous humour dynamics. More probably, these two mechanisms both cause the decrease in IOP, even if at a lower level, which we have found in the eyes with non-established findings of CPI.

Consequently, the IOPs of patients with lepromatous leprosy and borderline lepromatous leprosy were lower than in the normal group. This decrease in the IOP was more in the eyes where findings of CPI have been established, and this condition can be explained by inflammation decreasing the inflow. There was a decrease of IOP in the eyes in which objective findings as to

the CPI were not established as compared to the ones with established CPI symptoms. This suggests that hypotonicity related to leprosy cannot be attributed only to uveitis.

- 1 Brand ME, ffytch TJ. Eye complications of leprosy. In: Hastings RC, ed. *Leprosy*. Edinburgh, London: Churchill-Livingstone, 1985; 223-42.
- 2 Karaçorlu MA, Çakiner T. Lepre hastalığında göz problemleri. In: Saylan T, Süttaş M, Yaylacık Matbaası, eds. *II. Ulusal Lepre Semineri*. İstanbul: 1986: 99-107.
- 3 Brandt F, Malla OK, Anten JGF. Influence of untreated chronic plastic iridocyclitis of intraocular pressure in leprosy patients. *Br J Ophthalmol* 1981; 65: 240-2.
- 4 Aytekin H, Saylan T. Türkiye'de lepra (I). In: Saylan T, Süttaş M, Yaylacık Matbaası, eds. *II. Ulusal Lepre Semineri*. İstanbul: 1986: 51-63.
- 5 Jopling WH. *Handbook of leprosy*. 2nd ed. London: Heinemann, 1978: 18-41.
- 6 Ridley DS. Lepre histolojisinin uygulanması, tanı, sınıflandırma ve reaksiyonlar. In: Saylan T, Süttaş M, Yaylacık Matbaası, eds. İstanbul: 1986: 90-1.
- 7 Kozakoğlu H, Akşık K. Behçet Hastalığında hümeur aköz dinamiğinin incelenmesi. *Deri Hastalıkları ve Frengi Arçivi* 1986; 20: 127-37.
- 8 Oğuz V, Pazarlı H, Abidin S, Özyazgan Y. Evaluation de la relation entre le nombre d'attaques et le glaucome secondaire de la maladie de Behçet. *Bull Soc Ophthalmol Fr* in press.
- 9 Slem G. Clinical studies of ocular leprosy. *Am J Ophthalmol* 1971; 100: 431-4.
- 10 Karaçorlu M, Süre Z, Çakiner T, Hanyaloğlu F, Saylan T, Mat C. Pupil cycle time and early autonomic involvement in ocular leprosy. *Br J Ophthalmol* in press.

MINI REVIEW

The continuing challenge of ocular leprosy

The timely resurgence of interest in ocular leprosy noted in this journal a year ago continues,¹ as witnessed by the number of clinical papers from various centres which have recently appeared in the ophthalmic literature and the emphasis that is now being placed on measures for the prevention of blindness.² Apart from being one of the oldest infections known to man, leprosy is still the systemic disease with the highest incidence of ocular complications. Epidemiological studies of these have always proved to be difficult to obtain, and estimates of important aspects of the disease such as blindness rates and the prevalence of sight threatening lesions may fall wide of the mark.³

Ocular involvement in leprosy depends on a number of internal and external factors which may vary, not just within ethnic groups and geographic regions, but also from community to community. These factors include such variables as the age, race, and sex of the individual, the type of leprosy, its duration, therapy, and status. To these must be added the influence that the climate, environment, occupation, and social status have on the disease, and, most important of all, what measures to prevent eye complications are undertaken locally. Ocular leprosy is after all the archetypal preventive disease, and simple treatment at an early stage will usually avoid major irreversible damage later. This will be reflected by blindness and disability rates from different centres. Indeed, analysis of data derived from regional studies on the prevalence of eye complications often gives a very good idea of what services for leprosy are available in the community and how effective they are.

The problems of gathering information on the prevalence of eye complications in leprosy are further hindered by difficulties in estimating the actual numbers of patients with the disease. Many affected individuals do not come forward for treatment and therefore do not appear on registers until quite late in the course of disease. This is often due to ignorance, or it may reflect the social stigma that still exists throughout the world. The figures are further distorted by the WHO policy of deregistering patients once they have completed multidrug therapy and have satisfied the criteria for cure – a policy that has many pitfalls from the ophthalmic point of view. It is not therefore difficult to see why hard epidemiological data on the prevalence of ocular complications of leprosy are scarce, and knowledge on their incidence is almost non-existent.

A large multicentred study of ocular involvement in the disease, which included information on more than 3000 patients obtained by simple standardised examination techniques from over 30 centres in the world, showed that 5.5% of patients examined had bilateral corrected vision of less than 3/60 and were therefore blind by WHO definition, and 7.0% had vision less than 6/60, classified as having severe visual impairment. The same study demonstrated that 21.3% of patients had potentially sight-threatening lesions, defined as conditions likely to lead to visual loss unless preventive treatment was instituted.⁴ A parallel study on 354 patients who had been discharged from care having completed multidrug therapy, showed a prevalence of 24.3% with potentially sight-threatening lesions,⁵ and this raises the important point that in a considerable number of patients 'cure', as defined by the WHO, does not guarantee freedom from eye complications, and many patients may face increasing ocular problems

unless they are adequately supervised by leprologists after completing therapy.

Epidemiological information is therefore still lacking. But, if the global leprosy population is taken to be between 10 and 12 million,⁶ the disease ranks as one of the major causes of world blindness, likely to increase proportionally as others such as trachoma, xerophthalmia, and onchocerciasis become contained by modern therapy and public health measures.

The numbers, however, do not give the whole story. Leprosy is a unique condition, not least because of its social stigma, which evokes almost mediaeval sentiments in many countries, condemning the patient to become a member of one of the most disadvantaged groups in society. It is also a crippling disease. The nerve damage which is a feature of all forms of the condition, but particularly affects multibacillary (MB) patients, destroys tactile sensation, decreases mobility, and causes the familiar skeletal deformities. Loss of vision in these patients is a major event in this downward sequence of disability and frequently renders the patient entirely dependent on others. 'Blindness in the individual who has normal skin sensitivity is enough of a handicap, but in one who has lost that faculty it is disastrous. Few have the resources, material, mental or spiritual, to live with it.'⁷

The greatest current tragedy in this disease is that most of the ocular complications that lead to visual loss can be avoided by simple therapeutic measures requiring little more than adequate supervision, patient education and common sense. The role of the ophthalmologist should therefore be extended to one of a teacher, persuading leprologists and field workers and even fellow ophthalmologists, that leprosy is an ocular disease, that the eyes need supervision, not necessarily with sophisticated instruments, and that a mechanism for rapid referral to an ophthalmic centre should be available when serious sight-threatening complications develop.

Ocular involvement in leprosy occurs at several levels with differing effects on vision. In general the patients with the paucibacillary form, representing the tuberculoid and borderline-tuberculoid cases under the Ridley-Jopling classification,⁸ are affected through loss of lid function and corneal hypoaesthesia, whereas multibacillary patients, representing lepromatous, borderline-lepromatous, and mid borderline cases suffer complications through these as well as from direct infiltration of organisms into the anterior segment, inflammatory reactions, and damage to the adnexae.

Not surprisingly the many influential factors that determine which patients are at risk give rise to a variety of ocular manifestations, several of which do not threaten vision, but may indicate significant ocular involvement. They include such findings as madarosis, opaque corneal nerves, superficial stromal keratitis, and iris pearls.

Most of the visual impairment and blindness results from four main causes which may be isolated but often occur together: lagophthalmos leading to exposure keratopathy, corneal hypoaesthesia leading to ulceration, acute or chronic iridocyclitis, and secondary cataract.

LID INVOLVEMENT

The lower lid is affected through paralysis of the maxillary

branch of the facial nerve, giving rise to a reduction or failure of lid closure, with the consequent deleterious effect on protection of the cornea and lacrimal drainage. It occurs in all forms of leprosy, either as an acute event during a reversal reaction or over a long period of time. Immediate treatment of the acute stage with systemic steroids, thalidomide, or clofazamine will often lead to recovery or improvement of function.

In chronic cases, or in those which do not respond to medical therapy, it is often necessary to perform surgery on the lid, either in the form of a lateral tarsorrhaphy or by more sophisticated operations such as the tarsal strip procedure or temporalis transfer. Whereas tarsorrhaphy and some of the simpler lid surgery can be carried out by leprologists and field workers, procedures such as temporalis transfer require more expertise and usually involve an ophthalmologist.

The risk from lagophthalmos is always one of exposure keratopathy, particularly if the cornea already has diminished sensation. Monitoring of lid function by the leprologist and patient is an important preventive measure, and simple ways of protecting the eye can effectively reduce the incidence of corneal problems. Recent work by Hogeweg *et al.*⁹ on the relationship between the position of facial patches during erythema nodosum leprosum (ENL) reactions, and the subsequent development of lagophthalmos has considerably helped to identify those patients most at risk.

CORNEAL INVOLVEMENT

Corneal sensation is affected in all forms of the disease, and when hypoaesthesia accompanies impaired lid closure the eye is at high risk. Impaired corneal sensation predisposes to corneal damage as well as disturbing the normal epithelial metabolism, and the complications of corneal ulceration and opacification account for a significant proportion of blindness in leprosy. Diminished corneal sensation may well be an indicator of ocular pathology elsewhere as shown by the frequency with which it occurs in association with major ocular damage from the disease.¹⁰

Treatment consists of simple measures to protect the cornea at an early stage of the condition, and therefore detection of those eyes at risk is an important aspect of management. This is the combined responsibility of the leprosy worker and patient, since in the later stages the problems of dense vascularised corneal opacities may be insurmountable even with the most sophisticated surgical techniques.

IRIS INVOLVEMENT

Invasion of the iris and ciliary body by *Mycobacterium leprae* occurs exclusively in the multibacillary form of the disease. Acute iridocyclitis is often a feature of the ENL reaction and has all the signs of iritis due to any other cause except that pain and discomfort may not be so prominent. Conventional treatment with steroids and mydriatics is required, and field workers and leprologists need to be instructed in the early recognition and management of the condition.

Chronic iridocyclitis remains the enigma of this disease, though knowledge of the subject has increased considerably over the last decade. It is now accepted that organisms lodge in the iris and ciliary body at an early stage in lepromatous

leprosy, and attempts are being made to detect this involvement by measuring various types of pupil reactions such as the pupil cycle time, light/dark reactions, and pharmacological responses.¹¹ Other studies have analysed the effect of the disease on the ciliary body, manifested by a progressive lowering of intraocular pressure and alteration in postural responses.¹² Most authors now recognise that chronic iridocyclitis in multibacillary leprosy has neuromuscular elements, with primary involvement of the autonomic nerves, particularly the sympathetic fibres in the iris and ciliary body. This may raise the possibility of pharmacological treatment at an early stage to prevent the chronic immobile miotic pupil that characterises the end stage of the disease, and which can at present be overcome only by surgical intervention or photocoagulation.

CATARACT

The question of 'leprosy cataract' has yet to be solved. The disease is endemic in most countries where cataract is a major problem, and certainly data collected in surveys show that many patients have poor vision related to lens opacities without any signs of ocular leprosy. There is however a reported high prevalence of cataract in MB cases completing multidrug therapy,³ and this merits further study. Sadly the stigma of the disease that still exists in many countries often excludes the leprosy patient with cataract from receiving the surgical services that are available to other members of the community.

Cochrane in 1956¹³ described leprosy as 'the most thrilling and exciting adventure on which any medical man can embark', and the hyperbole 35 years ago was understandable. Our knowledge of the intricacies of the disease as it affects the eye is still increasing, but more clinical and laboratory work is needed. As we move forward into the new century there are still research efforts to be expanded, therapies to rationalise, prejudices to overcome, and challenges to meet in this ancient disease.

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- 1 ffytche TJ. Importance of early diagnosis in ocular leprosy. (Editorial.) *Br J Ophthalmol* 1989; 73: 939.
- 2 Courtright P, Johnson GJ. *Prevention of blindness in leprosy*. London: International Centre for Eye Health, 1988.
- 3 Courtright P. Defining the magnitude of ocular complications from leprosy: problems of methodology. *Int J Lepr Other Mycobact Dis* 1988; 56: 566-73.
- 4 ffytche TJ. The prevalence of sight-threatening lesions in ocular leprosy. *Proceedings of XXVth International Congress, Singapore 1990* (in press).
- 5 ffytche TJ. Residual sight-threatening lesions in patients completing multidrug therapy and sulphone monotherapy. *Lepr Rev* (in press).
- 6 World Health Organisation Expert Committee on Leprosy. *WHO Tech Rep Ser* 1988; 768: 9.
- 7 Brand M. The care of the eye. *The Star*. Carville, LA: 1980.
- 8 Ridley DS, Jopling WH. Classification of leprosy according to immunity. *Int J Lepr Other Mycobact Dis* 1966; 34: 255-73.
- 9 Hogeweg M, Kiran KU, Suneetha S. The significance of facial patches and type 1 reaction for the development of facial nerve damage in leprosy. *Lepr Rev* (in press).
- 10 Karacorlu M, Cakiner T, Saylan T. Corneal sensitivity and correlations between decreased sensitivity and anterior segment pathologies in ocular leprosy. *Br J Ophthalmol* (in press).
- 11 Lewallen S, Courtright PD, Ho-Sung Lee. Ocular autonomic dysfunction and intraocular pressure in leprosy. *Br J Ophthalmol* 1989; 73: 946-9.
- 12 Hussein N, Courtright PD, Ostler HB, Hetherington J, Gelber RH. Low intraocular pressure and postural changes in intraocular pressure in Hansen's disease. *Am J Ophthalmol* 1989; 1: 80-4.
- 13 Cochrane RG. Leprosy in Korea. *Lepr Rev* 1956; 27: 1-19.

CASE REPORT

Flecked retina associated with ring 17 chromosome

S J Charles, A T Moore, B C C Davison, H M Dyson, L Willatt

Abstract

We report the case of a mentally retarded male with a ring 17 chromosome who had subretinal drusen-like deposits in each eye. This is the second report of flecked retina in a patient with ring 17 chromosome, suggesting that there may be a causal relationship between abnormalities of chromosome 17 and retinal pigment epithelial or photoreceptor dysfunction.

the ring chromosome, rather than loss of chromatin.⁴

We describe a patient with ring 17 chromosome with a flecked retina, seizures, and café au lait spots in addition to mental retardation and short stature.

Case report

CLINICAL HISTORY

A 20-year-old male was reviewed who had been diagnosed 10 years previously as having peripheral neurofibromatosis (now classified NF-1). The parents were concerned lest any other family members might be at risk.

He was the first born child of non-consanguineous parents aged 21 and 18 years. His birth weight was 2.40 kg. Motor and mental development was retarded, and at age 5 he developed epilepsy. He attended a special school and at age 10 was admitted to hospital for investigation of epilepsy. At that time he had pigmented patches over his body. A diagnosis of NF-1 was made in view of his severe mental retardation, fits, and skin pigmentation. A skull x-ray and CT scan were normal. There was no family history of NF-1. Over the next 10 years his behavioural problems became more pronounced, necessitating long term inpatient care. Current medication included sodium valproate, carbamazepine, and thioridazine. Thioridazine had been taken for two years (not exceeding 75 mg/day), with a cumulative dose of approximately 35 g.

In inherited diseases cytogenetic abnormalities may provide the first clues to the location of the underlying genetic defect. For example, the association between interstitial deletions and ocular diseases such as retinoblastoma,¹ aniridia,² and choroideraemia³ has led to the localisation of the genetic loci for these conditions.

Ring chromosomes are thought to form by breaks occurring in both arms of a chromosome with fusion of the proximal ends leading to loss of the distal fragments.⁴ This loss of chromatin may give rise to major dysmorphogenesis and mental retardation, sometimes with specific phenotypic features associated with terminal deletions of these same chromosomes. However, in many patients with ring chromosomes that have no visible loss of chromatin there are only minor anomalies, and the main phenotypic features are growth failure and mental retardation, regardless of which chromosome forms the ring. This has led to the suggestion that part or all of the phenotype in such patients may result from the altered structure or instability at mitosis of

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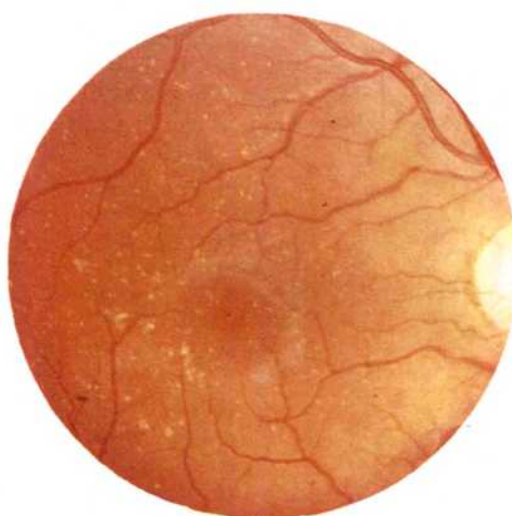


Figure 1A

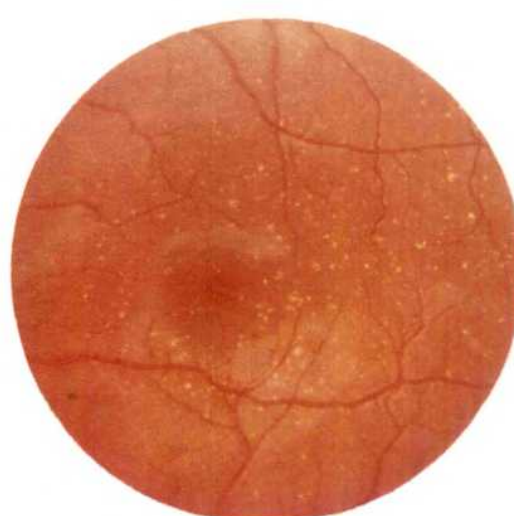


Figure 1B

Figures 1A, B Colour fundus photographs showing multiple drusen-like deposits at the posterior pole of each eye.

Figures 2A, B Fluorescein angiography showing slight masking associated with some deposits but no late hyperfluorescence.

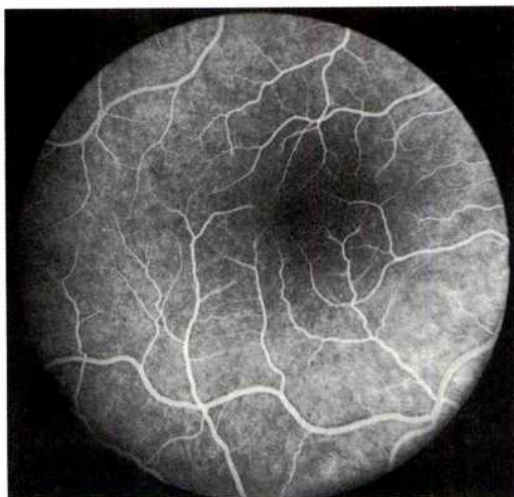


Figure 2A

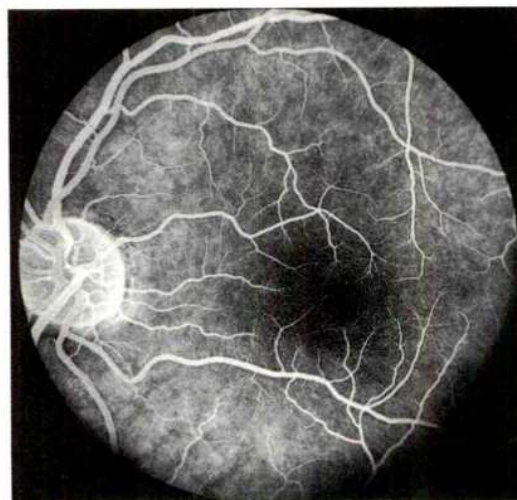


Figure 2B

EXAMINATION

At age 20 he was of short stature, 161 cm (<3rd centile), with a head circumference of 53 cm (10th centile), and weight 43.2 kg (<3rd centile). He had numerous café au lait spots, with four axillary freckles but no cutaneous neurofibromata. Visual acuity appeared to be good in each eye, with accurate assessment limited by the patient's mental retardation. The anterior segment was normal on examination, with no Lisch nodules. Retinal examination revealed multiple yellow flecks at both posterior poles at the level of the retinal pigment epithelium (RPE) similar to drusen (Figs 1A, B). Fundus fluorescein angiography (Figs 2A, B) showed normal choroidal and retinal vascular filling, with slight masking associated with some of the deposits at the posterior pole but no late hyperfluorescence.

Flash electroretinography (ERG) was normal bilaterally; the pattern ERG was found to be normal in one eye, but poor co-operation limited further investigations. Cytogenetic analysis revealed the karyotype 46,XY,r(17)(p13.3q25.3), with no visible deletion of the ring chromosome (Fig 3). Magnetic resonance imaging (MRI) of the brain gave normal results.

Parents and siblings were healthy, with no stigmata of NF and no retinal abnormalities. The mother's chromosomes were normal, but the father declined to have his examined.

Discussion

Ring chromosomes are uncommon, and to our

knowledge there have been only 11 reported cases of ring 17 chromosome. Common though non-specific features associated with this abnormality include mental and motor retardation, seizures, and short stature.⁵ Three cases of ring 17 chromosome have been described with Miller-Dieker lissencephaly,^{6,7} which has been mapped to the p13.3 portion of chromosome 17. Our patient had no brain abnormality on MRI scan. Multiple café au lait spots are seen in NF-1 and have also been described in patients with ring chromosomes, including chromosome 17. Although the NF-1 gene has been mapped to chromosome 17,⁸ the absence of neurofibromata or Lisch nodules⁹ in this case make the diagnosis of NF-1 unlikely.

The unusual eye findings in our patient resemble those in the 10-year-old girl with ring 17 chromosome described by Ono *et al.*¹⁰ She had numerous yellowish red retinal deposits, not associated with night blindness, and a normal ERG; her condition had been diagnosed as retinitis punctata albescens. This may not have been the correct diagnosis: retinitis punctata albescens has drusen-like deposits in the mid peripheral fundus with impairment of retinal function, and it is thought to be an early form of retinitis pigmentosa, not a distinct clinical entity.^{11,12} Our case has small yellow subretinal deposits at the level of the RPE or Bruch's membrane, which were similar in appearance to drusen but failed to fluoresce on fluorescein angiography. However, the degree of fluorescence of drusen may be related to their chemical composition,¹³ and some may show little fluorescence.¹⁴ Abnormal deposits in Bruch's membrane may cause a similar fundus picture.¹⁵ Thioridazine may cause a pigmentary retinopathy, rather than drusen-like change, which has not been reported with the low dosage used in this case.¹⁶ We consider that our patient and that of Ono *et al* have the same retinal dystrophy and that it is related to their chromosomal abnormality.

The ophthalmic examination of mentally retarded patients, particularly in the presence of a chromosomal abnormality, may reveal relevant pathology. Some causes of flecked retina are known to be associated with crystalline deposi-

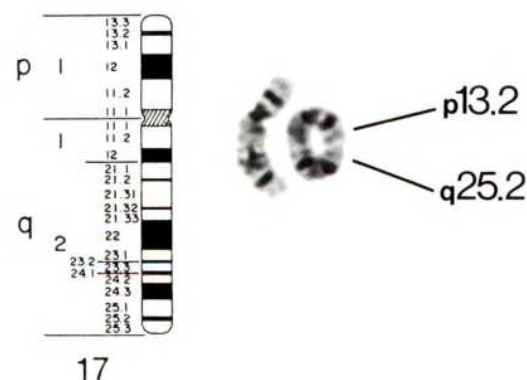


Figure 3 Idiogram and G-banded partial karyotype showing chromosome 17 in this patient. The bands p13.2 and q25.2 are indicated.

tion of an exogenous substance present in excess (as in oxalosis), but others (such as dominant drusen) may be caused by an isolated abnormality of receptor or RPE metabolism leading to an accumulation of abnormal material within the RPE or Bruch's membrane.¹⁶ This is the second report of flecked retina in patients with ring 17 chromosome, suggesting that loci on chromosome 17 may be involved in the regulation of retinal pigment epithelial or photoreceptor function. Most causes of flecked retina are inherited,¹⁷ but the underlying genetic defects are unknown. Chromosome 17 may be worthy of further investigation.

- 1 Yunis JJ, Ramsay N. Retinoblastoma and sub-band deletion of chromosome 13. *Am J Dis Child* 1978; 132: 161-3.
- 2 Riccardi VM, Sujansky E, Smith AE, et al. Chromosomal imbalance in the aniridia-Wilms' tumour association: 11p interstitial deletion. *Pediatrics* 1978; 61: 604-10.
- 3 Rosenberg T, Schwartz M, Niebuhr E, et al. Choroideremia in interstitial deletion of the X chromosome. *Ophthalmic Paediatr Genet* 1986; 7: 205-10.
- 4 Gardner RJM, Sutherland GR. *Chromosome abnormalities and genetic counselling*. Oxford: Oxford University Press, 1989: 89-92.
- 5 Borgaonkar DS. *Chromosomal variation in man. A catalog of chromosomal variants and anomalies*. 5th ed. New York: Alan Liss, 1989.
- 6 Stratton RF, Dobyns WB, Airhart SD, Ledbetter DH. New chromosomal syndrome: Miller-Dieker syndrome and monosomy 17p13. *Hum Genet* 1984; 67: 193-200.
- 7 Schroer RJ, Phelan MC. Miller-Dieker syndrome with ring 17, deletion 17p and monosomy 17. *Proc Greenwood Genetics Centre* 1987; 6: 41-3.
- 8 Barker D, Wright E, Nguyen K, et al. Gene for von Recklinghausen neurofibromatosis is in the pericentromeric region of chromosome 17. *Science* 1987; 236: 1100-2.
- 9 Huson SM, Jones D, Beck L. Ophthalmic manifestations of neurofibromatosis. *Br J Ophthalmol* 1987; 71: 235-8.
- 10 Ono K, Suzuki Y, Fuji I, et al. A case of ring chromosome E 17: 46,XX,r (17) (p13-q25). *Jpn J Hum Genet* 1974; 19: 235-42.
- 11 Newsome DA. Retinitis pigmentosa, Usher's syndrome, and other pigmentary retinopathies. In: Newsome DA, ed. *Retinal dystrophies and degenerations*. New York: Raven Press, 1988: 161-94.
- 12 Krill AE. Flecked retina diseases. In: Krill AE, ed. *Hereditary retinal and choroidal diseases*. Hagerstown: Harper and Row, 1977: 2.
- 13 Bird AC, Marshall J. Retinal pigment epithelial detachments in the elderly. *Trans Ophthalmol Soc UK* 1986; 105: 674-82.
- 14 Barondes M, Pauleikhoff D, Chisholm IC, Minassian D, Bird AC. Bilaterality of drusen. *Br J Ophthalmol* 1990; 74: 180-2.
- 15 Duvall-Young J, MacDonald MK, McKechnie NM. Fundus changes in (type II) mesangiocapillary glomerulonephritis simulating drusen: a histopathological report. *Br J Ophthalmol* 1989; 73: 297-302.
- 16 Gass JDM. *Stereoscopic atlas of macular diseases*. St Louis: Mosby, 1987.
- 17 Moore AT. Flecked retina syndromes. In: Taylor D, ed. *Paediatric ophthalmology*. Oxford: Blackwell, 1990; 27: 7.

LETTERS TO THE EDITOR

'Cutting hook' modification of a standard 19 gauge green needle

SIR,—Tight sutures tend to 'cheese wire' into the cornea with time in such a way that they become difficult to pick up and then cut in a controlled manner during their removal with a standard green needle. A modification is described below in which a conventional needle is fashioned into a cutting hook to facilitate the removal of such sutures.

The anterior portion of the bevel of a standard green needle is bent until the tip makes an angle of approximately 30° with the line of the shaft. This can be done using needle holding forceps. Alternatively, the tip of the needle may simply be compressed against its plastic sheath to fashion the shallow hooked profile required.

The blunt convexity of the hooked bevel is used to compress to cornea immediately proximal to the suture, allowing the point of the needle to slide beneath without snagging the adjacent stroma. Now resting in the crutch of the hook, the suture is lifted clear. A gentle to-and-fro motion is then employed to tease the suture clear of the epithelium along the full length of its superficial portion, before inclining the sharp edge and cutting so as to leave a convenient proud end ready to be grasped with fine blocked forceps.

While it is not difficult to remove loose or broken stitches with conventional methods, tight sutures causing refractive problems tend to 'cheese-wire' into the cornea with time, becoming less accessible. Although a tight suture will sink through the corneal epithelium, the stromal layers are merely compressed (in the straightforward case where stromal integrity is not affected by any melting process). Hence the superficial portion of a tight suture comes to lie in a furrow of compressed stroma. To undermine such a suture a straight needle must be inclined downwards into the cornea, and will thus tend to 'snag' the stroma on the other side of the stitch (Fig 1).

This has several disadvantages. Primarily, the stitch cannot be picked up cleanly. The needle must either be forced through the stroma or retracted so that the suture rests on its very tip. This often leads to the suture being cut prematurely without leaving a convenient proud end, in the latter case because an attempt is made to elevate the suture on the sharp point of the needle; whereas with the former approach the force required to disrupt the snagged stroma is such that the elastic recoil of the needle's shaft, once the stroma is breached, will flick the bevel through the suture—again leaving the cut ends partly buried in the epithelium and difficult to grasp.

By compressing the furrowed stroma immediately proximal to a tight suture with the blunt convex aspect of a needle bent at its tip as described above it is possible to undermine the suture with the point of the needle inclined tangentially or away from the globe (Fig 2).



Figure 1 A schematic illustration of the unmodified needle snagging the stroma distal to the suture being undermined.

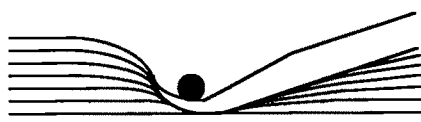


Figure 2 The tendency for stromal snagging is minimised by using the blunt convexity of the modified needle to compress the furrowed stroma proximally before sliding beneath the tight suture with needle's tip inclined tangentially or away from the globe.

The tendency to snag the stroma distally is thus minimised, allowing the stitch to be picked up cleanly. As it is elevated safely in the crutch of the 'hook', the tendency to cut the suture prematurely is also minimised.

Conventional straight needles were not designed specifically with a view to cutting corneal sutures. A simple modification, a shallow bend in the tip of the bevel to fashion a 'cutting-hook,' facilitates a better controlled and less traumatic execution of this task.

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Safety of intraocular lenses

SIR,—Your editorial, 'How safe are intraocular lenses',¹ was extremely interesting and timely. It is ironical, however, that another severe complication of intraocular lenses in diabetics, namely rubeotic glaucoma, was reported in the same issue² and received no editorial comment.

These two cases, reported by Prasad *et al*, point out the potential for disastrous results in patients with diabetes and non-proliferative retinopathy. Whereas there may not be an epidemic of bullous keratopathy on the way, even a few sporadic cases of neovascular glaucoma after posterior chamber intraocular lens implantation deserve our special attention.

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- 1 Smith R. How safe are intraocular lenses? *Br J Ophthalmol* 1990; 74: 257.
- 2 Prasad P, Setna PH, Dunne JA. Accelerated ocular neovascularisation in diabetics following posterior chamber lens implantation. *Br J Ophthalmol* 1990; 74: 313-4.

*I am obliged to Professor Kreiger for his comments on my editorial. I should explain that editorial comment in the *BJO* is usually directed to one particular paper. For logistical reasons we are not always sure that another paper somewhat in the same general area as the one being written about will appear in the same issue. We only comment on a group of papers if they are closely related to one another, in which case we deliberately arrange for them to be published together. In the case in question, the safety of intraocular lenses, the paper by Prasad *et al* mentioned by Professor Kreiger on rubeosis following cataract extraction did not seem to us to be close enough to the paper

dealing with corneal endothelial changes to warrant its inclusion in the editorial comment. It is well known that rubeosis can follow cataract extraction in diabetics, and I see no evidence in the paper by Prasad *et al* that the IOL played a leading role. However, I entirely agree with Professor Kreiger that the paper reminds us that, although rubeosis is more likely to follow intracapsular than extracapsular extraction, nevertheless the latter technique, whether an IOL is implanted or not, is clearly not 100% safe as far as rubeosis is concerned. —REDMOND SMITH.

Drop sizes of commonly used topical β blockers

SIR,—Drop size may be an important determinant of systemic adverse reactions to topical β blockers, since the volume of drops is large in relation to tear volume. Drop size is said to be about 50 μ l, whereas the volume of tears is typically about 7 μ l; 1 μ l in the precorneal tear film and 3 μ l in each of the tear menisci. The excess passes rapidly down the nasolacrimal duct,¹ where it can be rapidly absorbed across the nasal mucosa into the systemic circulation, avoiding first pass metabolism in the liver. It has been shown that small concentrated drops maintain equivalent tear film concentrations despite containing a smaller total amount of the active ingredient.¹ Drop size is mainly determined by the dimensions of the dropper tip. A nozzle with a wide bore and a thick wall produces bigger drops than one with a narrow bore and a thin wall.²

Drop size was determined by squeezing 10 drops on to the pan of an electronic top pan balance. This was repeated five times for each bottle, and for each β blocker tested two different bottles were used. It is assumed that the density of the drops is the same as water, so that weight in milligrams can be converted into volume in microlitres. Since they are only very dilute solutions this is likely to be true. Mean drop sizes are as follows (SD in parentheses):

Glauline 0.3%	25.6 (0.9) μ l
Glauline 0.6%	26.1 (0.4) μ l
Glauline 0.1%	27.7 (0.7) μ l
Timolol 0.25%	32.6 (0.8) μ l
Timolol 0.5%	34.0 (0.9) μ l
Teoptic 1.0%	33.4 (0.4) μ l
Betagan 0.5%	40.0 (2.2) μ l
Glauline 0.6% in a Betagan bottle	32.5 (1.0) μ l

Betagan (levobunolol) produced the largest drops. This may be related to its formulation in Liquifilm, which makes it more viscous and thus increases drop size. In keeping with this, when the Betagan bottle was filled with Glauline 0.6% the drops were smaller.

These figures are an estimate only, but at present are the best information available. Manufacturers should state drop size on the bottle and hopefully compete to produce bottles which consistently deliver smaller drops combined with ease of use.

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- 1 Shell JW. Pharmacokinetics of topically applied drugs. *Surv Ophthalmol* 1982; 26: 207-18.
- 2 Brown RH, Hotchkiss ML, Davis BE. Creating smaller eye drops by reducing eye dropper tip dimensions. *Am J Ophthalmol* 1985; 99: 460-4.

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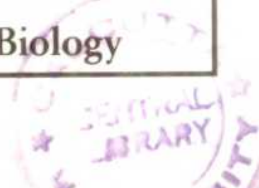
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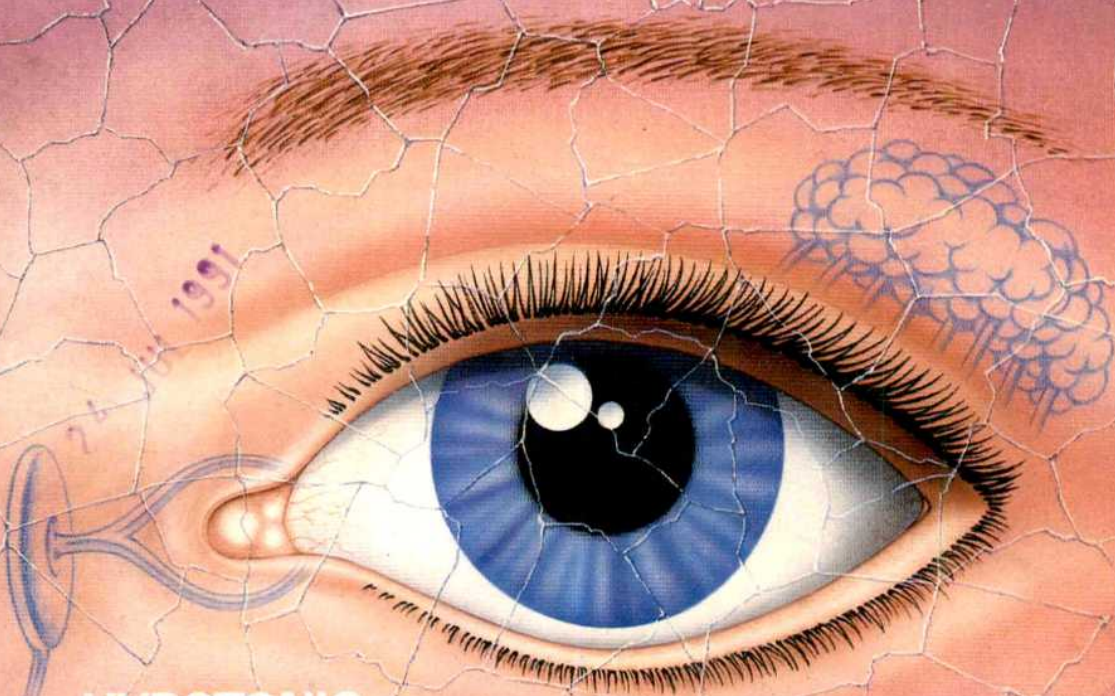
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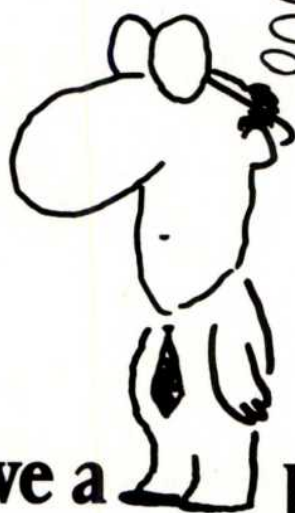
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zeman, E. *et al.*, Am J Ophthalmol 1982; 94 (3): 318-327. 2. Rakofsky S.I. *et al.*, Ophthalmology 1989; 96 (1): 8-11. 3. Mandel, T. *et al.*, Am J Ophthalmol 1986; 101: 298-304.



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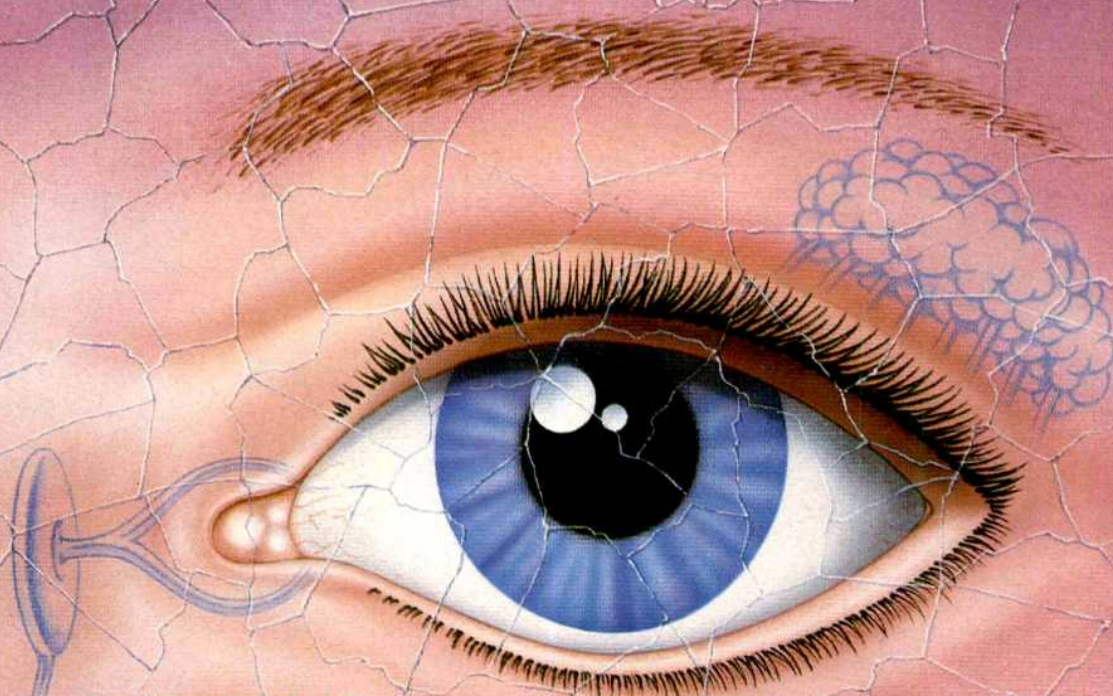
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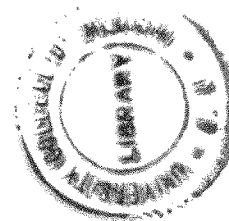


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BRITISH JOURNAL OF OPHTHALMOLOGY



Editorial

An adjunct to local anaesthesia

The subject of local and in particular retrobulbar anaesthesia for ophthalmic surgery has cropped up several times recently in the pages of the *BJO*. A general discussion on the relative merits of local (LA) and general (GA) anaesthesia for ophthalmic surgery would probably reveal large differences in routine practice from surgeon to surgeon and even from hospital to hospital, differences which would not be too easy to justify to an inquisitive lay administrator who had worked out that one or the other was the cheaper without apparently being any less effective. To such an observer the puzzling difference in LA/GA rates from surgeon to surgeon might appear to be based on little more than idiosyncratic personal preferences without obvious scientific justification. But nevertheless there is no doubt that preferences are strongly held and are based to some extent on previous training but also on other factors.

Many such factors influence surgeons in their choice of LA or GA: fear of eye movements during surgery, 'positive vitreous pressure' due to extraocular muscle spasm or concealed retrobulbar haemorrhage, and overt retrobulbar haemorrhage, are examples of worries about LA. As well as these possibilities there is the underlying anxiety that the anaesthesia will be incomplete, causing distress to both patient and surgeon, or that it will not last long enough, adding further to the surgeon's unease. (It should perhaps be noted in passing that the fear of retrobulbar haemorrhage can easily be avoided by not giving a retrobulbar injection, as reported recently.^{1,2})

The most obvious objection to GA is that it involves another highly trained individual, the anaesthetist, who might be better employed elsewhere in the hospital for forms of surgery where GA is thought to be essential. In times of financial stringency in medicine in virtually all parts of the world this aspect needs to be taken seriously, and the time might well come in the UK, and may have already have arrived in other parts of the world, when the insurers or

government agencies funding medicine start asking awkward questions as to the absolute necessity for GA in ophthalmic surgery, and not only for day surgery but for inpatient surgery as well.

Clinical disadvantages of GA concern its possible effect on the general well-being of the patient. In spite of improvements in technique whereby anaesthesia is confidently given to patients with the frailest of constitutions and at practically any age, nevertheless a lingering doubt remains in the minds of some surgeons that GA may not always be quite safe, though others clearly have complete confidence.³

An adverse influence on the conduct of an operation by GA rarely occurs, though there is always the outside possibility of something going wrong with the depth of anaesthesia, so that the patient coughs, gags, or even wakes up. Another minor disadvantage of GA is that it involves more preoperative organisation and more equipment, but these points are really part of the administrative implications mentioned above.

If a trend towards more widespread use of local anaesthesia does develop, then it follows that better techniques will also be sought. One such improvement is noted in this issue in a paper by Dr P Sunderraj and colleagues. A technique is described whereby the initial discomfort of the needle puncture of the retrobulbar injection and hence the injection itself may be reduced. (The same would presumably apply to percutaneous peribulbar injections.) Any step in this direction is to be welcomed, and the authors are to be congratulated on a useful contribution.

REDMOND SMITH

1 Redmond RM, Dallas NL. Extracapsular cataract extraction under local anaesthesia without retrobulbar injection. *Br J Ophthalmol* 1990; 74: 203-4.

2 Smith RJH. Cataract extraction without retrobulbar anaesthetic injection. *Br J Ophthalmol* 1990; 74: 205-7.

3 Steele A. Local anaesthesia for cataract surgery. (Editorial.) *Br J Ophthalmol* 1990; 74: 195.

ORIGINAL ARTICLES

A double-masked evaluation of lignocaine-prilocaine cream (EMLA) used to alleviate the pain of retrobulbar injection

Palaniswamy Sunderraj, John Kirby, Patrick W Joyce, Allan Watson

Abstract

A randomised, placebo controlled, double-masked study was undertaken in 115 patients undergoing cataract surgery to assess the efficacy of the anaesthetic cream EMLA (eutetic mixture of local anaesthetic, lignocaine-prilocaine) in alleviating the pain of retrobulbar injection. Sixty three patients received the EMLA cream and 52 the placebo cream. The pain was assessed objectively by the anaesthetist, who observed the reaction of the patient on needle insertion, and subjectively by the patient. Significantly lower pain scores were recorded in patients treated with EMLA cream (anaesthetist's observation: $p < 0.01$, patient's assessment: $p < 0.006$). No patients experienced serious side effects in either treatment group.

Day case cataract surgery is now commonly performed in the United States of America and Canada.¹ It is becoming commoner in the United Kingdom, with increasing use of local anaesthesia, either retrobulbar or peribulbar.²⁻⁴ Both retrobulbar and peribulbar injections which involve insertion of a needle through the skin of the periocular region can be painful procedures. Pain increases the anxiety of elderly patients undergoing cataract surgery, causing the experience to be unpleasant for them and the procedure potentially more difficult for the surgeon.

A topical preparation which can be applied to the skin without discomfort and which alleviates the pain of needle insertion would be helpful to both patients and staff. The local anaesthetic cream EMLA (eutetic mixture of local anaesthetics) which contains a mixture of lignocaine and prilocaine has been shown to reduce the pain associated with skin puncture and other superficial skin procedures in both children and adults.⁵⁻¹² Local skin reactions have been minor and transient.⁵⁻¹² Previous studies, which have been concerned mainly with pain on venepuncture, have identified a minimum application period of 45 minutes in adults to ensure maximal analgesic effect.⁹ This study was performed to assess the efficacy of EMLA cream in alleviating the pain of retrobulbar injection and identify possible unwanted side effects of the preparation.

Patients and methods

One hundred and fifteen patients between the ages of 57 and 95 years who presented to the Department of Ophthalmology, Southport and Formby District General Hospital, for day case cataract surgery under local anaesthetic were included in the study. Informed, written consent was obtained from all the patients. The study protocol was approved by the Hospital Ethical Committee.

EMLA 5% cream consists of a mixture of lignocaine base 25 mg/ml (107 mmol/l) and prilocaine base 25 mg/ml (113 mmol/l). The remaining ingredients are an emulsifier, a viscosity increasing agent, and water. The placebo cream, a mixture of light liquid paraffin, white soft paraffin, and wool fat, was visually identical to EMLA.

The study was a double-masked comparison of EMLA cream with the placebo. The treatments were distributed at random, and at the end of the study 63 patients had received EMLA cream and 52 patients the placebo cream. Oral premedication was not used for any patient.

A thick layer of cream, about 2 ml, was applied in the ward by a nurse to the skin in the region of the outer half of the inferior orbital margin at least one hour preoperatively. The cream was covered with a Tegaderm (3M) occlusive dressing. Great care was taken while applying the cream and the occlusive dressing to prevent the cream from entering the eye. On the patient's arrival at the operating theatre anaesthetic room the occlusive dressing was removed and the cream wiped off with a dry swab. Local reactions, if any, were recorded by the person administering the retrobulbar injection, who was unaware of the identity of the topical cream.

Retrobulbar injections were performed with a 23 standard wire gauge, 30 mm long disposable needle. The needle was introduced at the junction of the lateral one-third and the medial two-thirds of the inferior orbital rim. Up to 5 ml of 0.5% bupivacaine hydrochloride with 1500 units hyaluronidase was slowly injected after aspiration to eliminate possible intravascular injection. This technique was used for all the study patients.

The person who administered the retrobulbar injection was required to make two assessments. The first was of the patient's reaction at the

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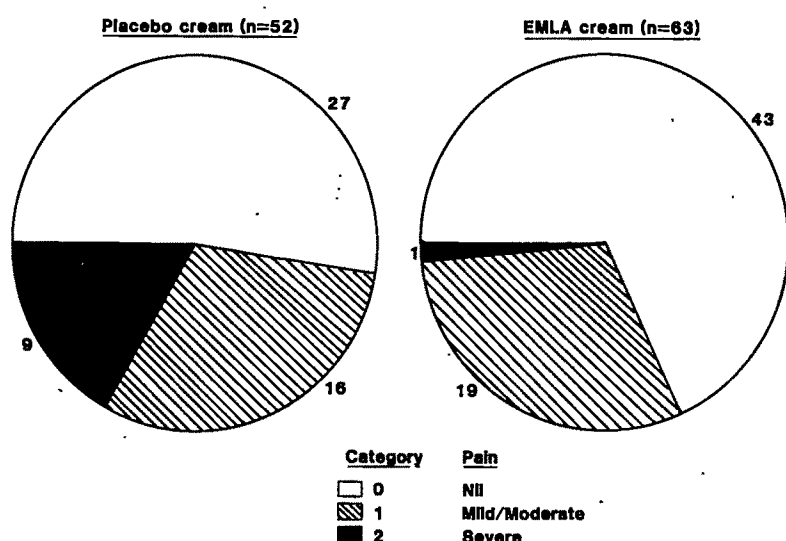


Figure 1 Pain on retrobulbar injection as determined by the anaesthetist.

moment of skin penetration, which was graded on the following scale:

- 0 (no pain) – no reaction to injection;
- 1 (mild or moderate pain) – transient grimace, slight groan or minor reflex movement;
- 2 (severe pain) – loud or continuous verbal complaint, intensive or continuous reflex movement.

The second was of the subjective intensity of the pain felt by the patient. The patients were requested to grade pain on a scale between 0 (no pain) and 10 (intolerable pain).

The statistical significance of the difference between the patients who received the EMLA cream and those who received the placebo was analysed by the χ^2 test for the results of the patient's reaction to the retrobulbar injection as observed by the anaesthetist. The Mann-Whitney test with rank sums and the unpaired t test were used for analysing the results of the patient's subjective assessment of pain.

Results

The results from 115 patients undergoing cataract surgery were analysed. No patient's results were excluded. There were 63 patients in the EMLA group comprising 21 males and 42

females, with a mean age of 78.2 (SD 7.6) years. Of the 52 patients in the placebo group 16 were male and 36 were female, with a mean age of 79.2 (SD 8.2) years. There was no statistically significant difference between the two groups in their baseline characteristics.

Fig 1 shows the patients' reactions to the retrobulbar injection as observed by the anaesthetist. Treatment with EMLA cream resulted in significantly less pain on retrobulbar injection compared with placebo ($\chi^2=9.36$, $df=2$, $p<0.01$).

Fig 2 shows the pain of retrobulbar injection subjectively assessed by the patients. The individual pain scores after the application of the placebo cream were scattered over the whole scale, while the majority of scores after EMLA cream were near the 'no pain' end of the scale. Patients who received EMLA cream (mean pain score 2.6, SD 1.9) scored significantly less pain compared with those who received the placebo (mean pain score 3.8, SD 2.3; Mann-Whitney test, $Z=2.812$, $p<0.006$; unpaired t test, $t=3.069$, $p<0.005$).

No significant local side effects were noted, and there were no cases of marked erythema, scaling, oedema, or allergic reaction in either the EMLA or placebo group. Some EMLA cream inadvertently leaked on to the eyes of three patients in the time between its application and the arrival of the patient at the operating theatre. All the three eyes showed congested conjunctiva with loss of the corneal epithelium in one eye. The latter could have been due to the preoperative ocular biometry or the EMLA cream. The placebo cream leaked on to the eyes of two patients. Of these, one eye was unaffected and the other had mild conjunctival congestion. All the above five eyes underwent uneventful cataract extraction with intraocular lens implantation.

Discussion

EMLA cream has proved to be effective in reducing the pain of venepuncture in both children and adults.²⁻⁴ It penetrates the intact skin and has been used successfully as a topical analgesic for superficial skin procedures,¹⁰ lumbar punctures,¹¹ and arterial cannulation.¹² Our study of elderly patients undergoing cataract surgery demonstrates the efficacy of EMLA cream in alleviating the pain of retrobulbar injection. This benefits the patient undergoing cataract surgery because it reduces anxiety, and the doctor because the retrobulbar injection is administered more easily if the patient does not react adversely to the needle puncturing the skin.

There were no unwanted local effects of any significance. Despite great care in application, the study creams leaked on to the eyes of five patients. The EMLA cream produced transient stinging, congested conjunctiva and possibly in one patient corneal epithelial denudation. However, uncomplicated cataract-intraocular lens surgery was possible in all the patients.

In conclusion, EMLA cream is effective in alleviating the pain of retrobulbar injection in patients undergoing cataract surgery. We now

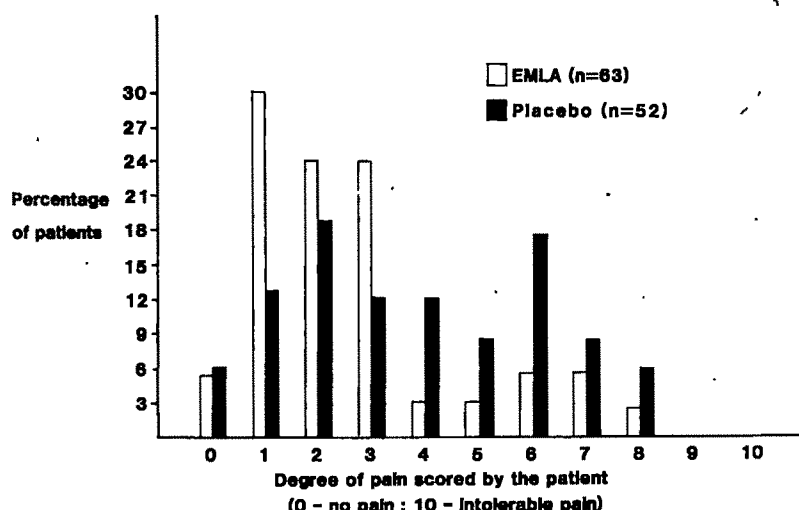


Figure 2 Pain on retrobulbar injection as indicated by the patient.

use this cream routinely for all patients undergoing intraocular surgery under local anaesthetic.

We gratefully acknowledge the administrative help of the nursing staff of the ophthalmic ward and the ophthalmic operating theatre. We thank Lisa Jones for typing the manuscript.

- 1 Severin SL. Out patient cataract surgery. *Semin Ophthalmol* 1986; 1: 130-5.
- 2 Ingram RM, Banerjee D, Traynor MJ, Thompson RK. Day case cataract surgery. *Br J Ophthalmol* 1983; 67: 278-9.
- 3 Davies PD, Limacher E, Powell K. Out-patient cataract surgery 1982-1986. *Eye* 1987; 1: 728-34.
- 4 Watts MT, Pearce JL. Day case cataract surgery. *Br J Ophthalmol* 1988; 72: 897-9.
- 5 Hallen B, Uppfeldt A. Does lidocaine-prilocaine cream permit pain-free insertion of intravenous catheters in children? *Anaesthesiology* 1982; 57: 340-2.
- 6 Hallen B, Carlsson P, Uppfeldt A. Clinical study of a lignocaine-prilocaine cream to relieve the pain of venepuncture. *Br J Anaesth* 1985; 57: 326-8.
- 7 Maunukela EL, Korpela R. Double-blind evaluation of a lignocaine-prilocaine cream in children *Br J Anaesth* 1986; 58: 1242-5.
- 8 Hopkins CS, Buckley CJ, Bush GH. Pain-free injection in infants. *Anaesthesia* 1988; 43: 198-201.
- 9 Ehrenstrom-Reiz GME, Reiz SLA, Stockman O. Topical anaesthesia with EMLA, a new lidocaine-prilocaine cream and the Cusum technique for detection of minimal application time. *Acta Anaesthesiol Scand* 1983; 27: 510-2.
- 10 Juhlin L, Evers H, Broberg F. A lidocaine-prilocaine cream for superficial skin surgery and painful lesions *Acta Derm Venereol (Stockh)* 1980; 60: 544-6.
- 11 Kapelushnik J, Koren G, Solh H, Greenberg M, Deveder L. Evaluating the efficacy of EMLA in alleviating pain associated with lumbar puncture; comparison of open and double-blinded protocols in children. *Pain* 1990; 42: 31-4.
- 12 Smith M, Gray BM, Ingram S, Jewkes DA. Double-blind comparison of topical lignocaine-prilocaine cream (EMLA) and lignocaine infiltration for arterial cannulation in adults. *Br J Anaesth* 1990; 65: 240-2.

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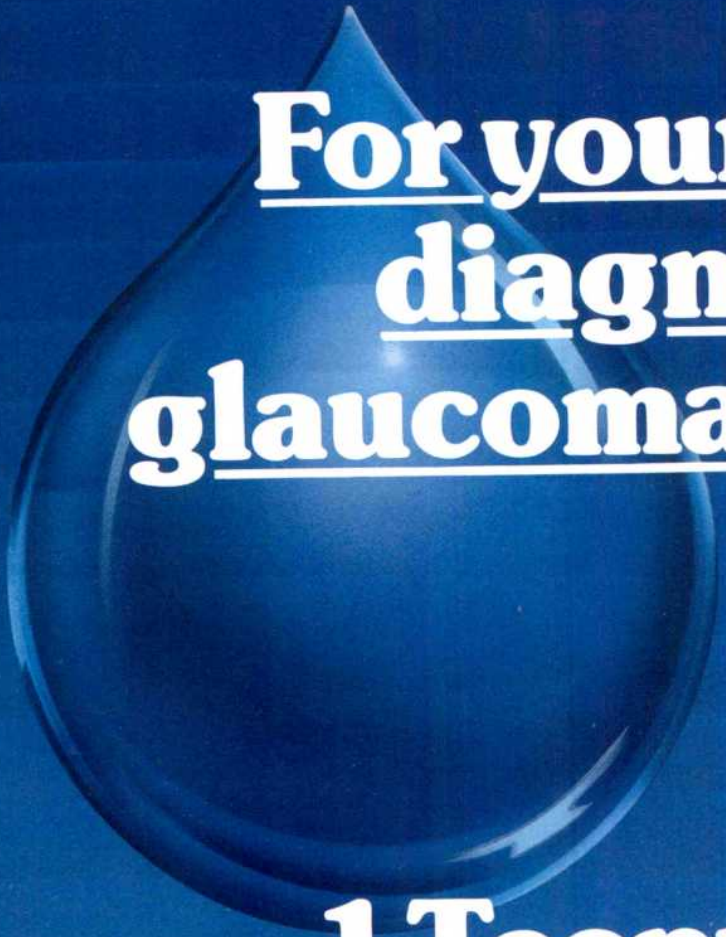
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References

1. Maclure, G.M. et al. 3rd Congress of European Glaucoma Society, 1988.
2. Kitazawa, Y. et al. Acta XXIV International Congress of Ophthalmology, 1983. P. Henkind (Ed), Lippincott, Philadelphia.
3. Hugues, F.C. et al. J. Fr. Ophthalmol. 1987; **10**, 8/9, 485-490.
4. Negishi, C. Acta Soc. Ophthalmol. Jpn. 1982; **85**, 57-66.
5. Scoville, B. et al. American Journal of Ophthalmology, 1988; **105**, No.2, 150-154.

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Symmetry of disciform scars in bilateral age-related macular degeneration

Michael J Lavin, Bora Eldem, Zdenek J Gregor

Abstract

The size of the final macular scar in subretinal neovascularisation (SRNV) is one of the most important determinants of final visual function in patients with subfoveal disease. We studied patients with bilateral macular scars from age-related subretinal neovascular membranes retrospectively in order to determine whether or not fellow eyes behave similarly. We found a significant correlation between eyes in terms of final scar size ($r=0.50$, $p<0.01$). We found that 50% of fellow eyes with large macular scars ($>3 \times 10^6 \mu m^2$) had similar sized lesions, while only 16% of fellow eyes with small macular scars ($<0.5 \times 10^6 \mu m^2$) had large scars ($p<0.01$). We discuss the significance of these findings in relation to the pathogenesis of subretinal neovascular membranes, and their implications for treatment.

Age-related macular degeneration (AMD) is the major cause of visual loss in the elderly.¹ Approximately 10% of patients with AMD suffer subretinal neovascular membrane (SRNVM) formation and its complications, though this is responsible for most of the legal blindness in this disease.² When eyes with similar visual acuities are compared, patients with SRNVMs have much poorer visual function than those with other forms of AMD.³ Since the quality of para-central visual function is related to the retinal distance from the fovea,⁴ and exudative AMD has a high incidence of bilaterality,⁵ we wished to know whether or not the retinal scar size resulting from exudative AMD was similar between eyes in bilateral cases. This could provide useful information on the likely visual prognosis in the good eye in individual patients and have important implications for possible treatment.

There is evidence that features of non-exudative AMD are symmetrical⁶ and that the type and extent of drusen formation is highly correlated between eyes in patients with non-exudative AMD.⁷ Although symmetry has been demonstrated for one complication of AMD, namely tears of the retinal pigment epithelium,⁸ it is not known whether or not the high degree of concordance seen in drusen is reflected in the behaviour of other exudative complications of AMD. Since SRNVMs form the bulk of cases of exudative AMD,⁹ we limited our study to cases with documented SRNVM formation.

While these SRNVMs may under some circumstances be amenable to laser treatment,^{10,11} a large number of SRNVMs are not treatable by conventional means.¹⁰ Since the final scar size, in

the presence of foveal involvement, is a major determinant of subsequent paracentral visual function,¹² some workers have suggested that ablation of subfoveal membranes may be justified in order to limit the final scar size and reduce the resultant scotoma^{13,14} when the fellow eye has a poor outcome from AMD. The final scar size resulting from SRNVMs can be highly variable. We wished to know whether or not it would be possible to identify factors indicating a high risk of large scars forming.

Material and methods

We performed a retrospective study of patients with bilateral disciform macular scars resulting from age-related macular degeneration. Consecutive patients with bilateral disciform macular scars were identified from a database of patients attending the Retinal Diagnostic Department at Moorfields Eye Hospital. Stereoscopic colour photographs and fluorescein angiograms were examined in order to determine eligibility. Patients were included in the study only if their bilateral macular scarring was the result of subretinal neovascular membrane formation secondary to age-related macular degeneration. Patients with pigment epithelial detachment were included if there was clear evidence of subretinal neovascularisation. Patients with atrophic macular lesions, or geographic atrophy, were excluded. Patients who had had laser photocoagulation to either eye at any time were excluded. A minimum duration of subretinal neovascularisation of six months was required.

Stereo colour photographs and fluorescein angiograms were examined independently by two observers (ZJG and MJL), and scar size was measured by a standardised photographic slide overlay.⁵ The scar size was ascertained from colour photographs and fluorescein angiograms by measuring from the edges of subretinal fibrovascular tissue. The extent of subretinal fluid or blood was not included in these measurements. The area of fibrosis apparent on the colour photographs was usually less than the area of neovascularisation visible angiographically, and where a difference existed the larger measurement was used. Area approximations were arrived at by multiplying the length of the longest axis of the scar with the scar diameter perpendicular to it.

A total of 100 patients with bilateral established macular scarring resulting from subretinal neovascularisation in age-related macular degeneration were identified. Of these, 19 patients were not included owing to inadequate follow-up, leaving a study population of 81 patients.

Interobserver agreement error was tested with

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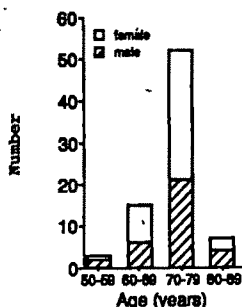


Figure 1 Age and sex distribution of patients. Accurate age data not available for 4 patients.

a random series of 10 eyes. Measurements were similar between two observers for 10 eyes, with no error exceeding 10%.

Results

The patients ranged in age from 54 to 86 years, with a mean of 69.7 (SD 17.0) years (Fig 1). Patients with large scar sizes ($>3 \times 10^6 \mu\text{m}^2$) tended to be older than those with small scars, but this difference was not statistically significant. Analysis of covariance found age was not a variable associated with scar size.

The distribution of scar size in our patients (Fig 2) appeared to have two peaks: an initial peak of under $0.5 \times 10^6 \mu\text{m}^2$ in area, accounted for 50/162 (30.9%) of eyes. While 28 eyes (17.2%) had scar sizes ranging between 0.5 and $0.99 \times 10^6 \mu\text{m}^2$, only small percentages of eyes fell in the intervening ranges of 1 to $3 \times 10^6 \mu\text{m}^2$ in area. A second peak was found in the 3 to $4 \times 10^6 \mu\text{m}^2$ range which accounted for 42/162 (25.9%) of eyes (Fig 2).

Scars of less than $0.5 \times 10^6 \mu\text{m}^2$ in area were found in 50 eyes of 36 patients. The distribution of scar sizes in the fellow eye of patients with one scar measuring less than $0.5 \times 10^6 \mu\text{m}^2$ is charted in Figure 3. In 38.8% (14/36) of fellow eyes, scars measured less than $0.5 \times 10^6 \mu\text{m}^2$, and 61.1% were less than $1 \times 10^6 \mu\text{m}^2$ in area. Only 16.7% (6/36) had large scar sizes ($>3 \times 10^6 \mu\text{m}^2$).

Scars measuring $3 \times 10^6 \mu\text{m}^2$ or more in area were identified in 42 eyes of 28 patients. The distribution of scar sizes in the fellow eye of patients with one scar measuring $3 \times 10^6 \mu\text{m}^2$ or more is charted in Figure 3. In 21.4% (6/28) the scar in the fellow eye measured less than $0.5 \times 10^6 \mu\text{m}^2$, and in 28.6% (8/28) measured less than $1 \times 10^6 \mu\text{m}^2$. In 50% (14/28) the fellow eye scar was 3 or more $\times 10^6 \mu\text{m}^2$ in area.

We compared the distribution of scar sizes in fellow eyes of eyes with small scars ($<0.5 \times 10^6 \mu\text{m}^2$) with that of fellow eyes of eyes with large scars ($>3.0 \times 10^6 \mu\text{m}^2$). The data summarised in Figure 3 were grouped into three size distributions ($<0.99 \times 10^6 \mu\text{m}^2$, 1.0 – $2.9 \times 10^6 \mu\text{m}^2$, and $>3.0 \times 10^6 \mu\text{m}^2$) to allow for small data sets in the mid range of sizes. A significant difference in distribution between the groups was found

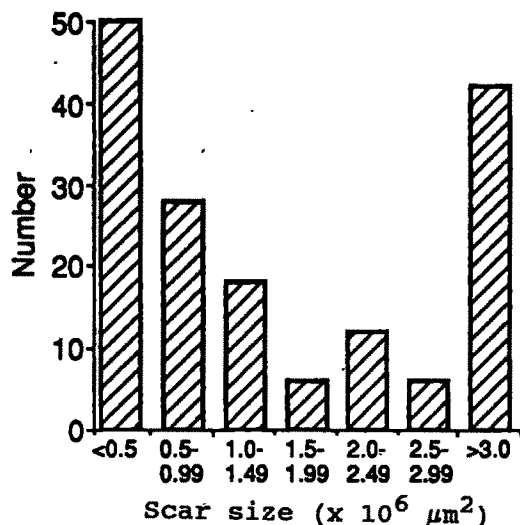


Figure 2 Distribution of macular scar sizes in all eyes.

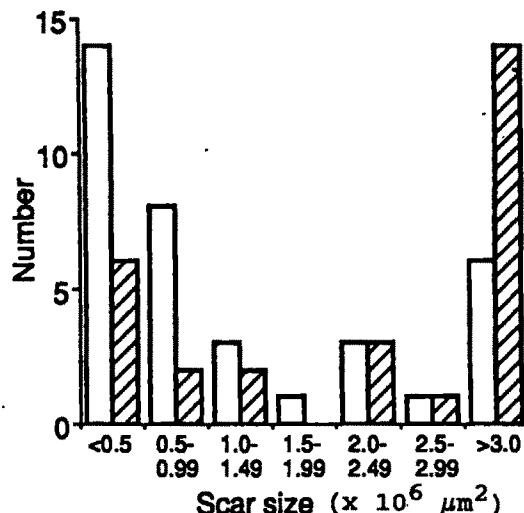


Figure 3 Fellow eyes of small scars compared with fellow eyes of large scars by scar size. ($\chi^2=20.07$, $=2$, $p<0.001$). □ = Fellow eye of small scar. ▨ = Fellow eye of large scar.

with the χ^2 test ($\chi^2=20.07$, 2 degrees of freedom, $p<0.001$).

Figure 4 demonstrates that a correlation exists between the scar size in one eye and the scar size in the fellow eye. Although a number of outliers exist, a clear uptrend is present ($r=0.53$, $p<0.001$; 95% confidence level for correlation coefficient: 0.37 – 0.77).

We also assessed the degree of concordance of scar size using the κ statistic.¹⁵ This produced a weighted κ score of 0.547 (standard error = 0.153), indicating a degree of concordance rated as 'fair to good'.¹⁶

We examined the scar sizes in 20 pairs of eyes with a minimum of six months' follow-up, and compared them with a group of 18 eyes with a minimum of three years' follow-up. There was no significant difference in the distribution of scar sizes between the two groups ($p=0.36$). We were concerned that eyes with a shorter duration of follow-up might have had evolving lesions which had not yet reached their final scar size. We re-examined the question of concordance of scar size for 43 patients with a minimum follow-

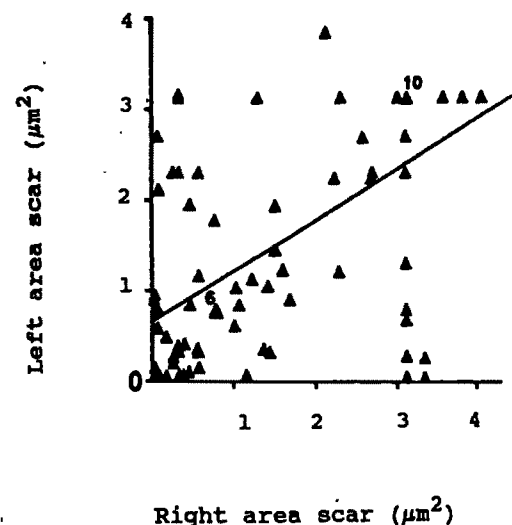


Figure 4 Area of scar: right and left eyes of pairs compared. Numbers on chart refer to number of pairs of eyes located at similar points. Line of best fit has been added ($r=0.53$, $p<0.001$; 95% confidence level for correlation coefficient: 0.37 – 0.77).

up period of 12 months, and found a weighted κ score of 0.68. The time of presentation did not appear to influence subsequent scar size – that is the first affected eye did not have a tendency towards larger or smaller scars.

We examined lesions for the presence of pronounced pigmentation, intraretinal exudate, and persistent subretinal fluid. We identified 17 eyes in which pigment was a major feature of the AMD lesion. In eight eyes (47%) the macular scar size was less than $1.5 \times 10^6 \mu\text{m}^2$, while only 12.7% eyes with no pigment epithelial hyperplasia had lesions of this size ($p < 0.001$).

Circinate exudate was identified as a major feature of macular scars in 14 eyes, 12 of which (85.7%) had lesions measuring more than $3 \times 10^6 \mu\text{m}^2$.

Discussion

We have found a relationship between the scar size of one eye and the size of the scar in the fellow eye of eyes with SRNVM secondary to AMD. This implies that factors peculiar to a particular patient have an important role in determining how advanced the process of subretinal neovascularisation and fibrosis may become. It has been noted that patients with AMD are significantly more likely to have a family history of central visual loss suggestive of AMD than controls.² That genetic factors may contribute to the risk of AMD is suggested by the report of monozygotic twins with similar AMD lesions.¹⁷ This is supported by the finding that patients with AMD may have raised serum caeruloplasmin levels, and that this abnormality may be familial.¹⁸ The lower incidence of AMD in Asians¹⁹ and blacks²⁰ provides further evidence for the importance of inherited factors.

Systemic associations with AMD have been documented, and these include elastotic degeneration of the dermis,²¹ reduced hand grip strength,² and cigarette smoking.² It is possible that the similarity in scar sizes between eyes in the same individual may reflect the effect of some underlying inherited or systemic factor on the behaviour of SRNVM complicating AMD.

Alternatively factors peculiar to the eyes, but symmetrical, may influence scar size. A recent study has found a marked degree of concordance in the characteristics of drusen of eyes with AMD in the absence of SRNV.* While our study shows a degree of concordance, it is lower than that found by Barondes *et al.*,* and it may reflect the multitude of factors involved in fibrovascular scar formation. Since drusen type determines the relative risk of SRNVM formation,^{22,23} the high degree of symmetry of drusen type and extent found by Barondes *et al.** may be a factor in the high frequency of bilaterality and the symmetry of SRNVM secondary to AMD.

We have noted that almost half the eyes (47%) with pigmented scars have lesions measuring less than $1.5 \times 10^6 \mu\text{m}^2$. The retinal pigment epithelium plays a part in regulating the behaviour of SRNVM complexes,²⁴ and it is possible that this could be a factor in determining the final scar size and the correlation between

eyes. It is not clear at what point in the evolution of a SRNVM this feature becomes evident, but this could have prognostic implications.

Most of the eyes with considerable exudation had large macular scars (85.7%), and this may reflect the activity of the underlying SRNVM, or its choroidoretinal vascular shunts. While a good degree of concordance of scar size between eyes was found for the study group as a whole ($\kappa = 0.54$), we found that the degree of concordance was increased when we considered only those patients with at least 12 months' follow-up ($\kappa = 0.68$). This implies that some of the variation between eyes may be attributed to lesions which are slowly evolving and have yet to reach their final scar size.

Our findings have implications for treatment of individual patients. It is not uncommon to encounter a patient with an established macular scar from SRNVM secondary to AMD in one eye, and a SRNVM within the foveal avascular zone in the fellow eye. In such patients treatment carries a significant risk of compromising foveal function.¹⁴ While SRNVMs with large vascular channels are thought to have slower growth,²⁵ a recent study could not identify any morphological features indicative of rapid growth.²⁶ Our results suggest that, in patients whose established macular scar is small, the risk of developing a large macular scar in the remaining eye is approximately 16%, and aggressive treatment in these patients may not be justified. By contrast, in patients with a large established scar the risk to the paracentral visual function of the fellow eye is considerable, since 50% develop large scars, and aggressive treatment in these cases could be considered.

A further clinical problem is that of the eye with a single large scar resulting from SRNVM secondary to AMD, and a fellow eye with AMD but no evidence of SRNVM formation. Previous studies have suggested that these eyes are exposed to a 7–15% cumulative annual incidence involvement of the fellow eye with SRNVM.^{5,27} This implies that 30–50% of fellow eyes would have suffered SRNVM at five years. Since 50% of these eyes will have large scars, 25% of the original group are likely to develop bilateral severely incapacitating macular lesions. If one arbitrarily defines a large scar as any lesion larger than $2.0 \times 10^6 \mu\text{m}^2$, then the percentage rises to 32%.

In a review of a sequential series of patients with SRNVM formation secondary to AMD, the majority had scar sizes larger than one disc diameter (68%).⁹ It is interesting to note a biphasic distribution of scar size in the study (Fig 2). This biphasic peak suggests that different factors determine whether an eye develops either a small or a large scar. Such an 'on or off' response is compatible with several types of cellular phenomena, and may be the end result of a retinal environment inhibitory to or stimulating SRNVM formation. In this light it is interesting to note that the retinal pigment epithelium may have a major role in regulating the activity of laser induced experimental SRNVMs²⁴ and of vascular endothelial cells.²⁸

Some evidence suggests that inflammatory and immunocompetent cells may play a part in

*Barondes MJ, *et al* unpublished.

the genesis of both the atrophic forms of AMD²⁹ and its neovascular complications.³⁰ Immunological responses vary markedly between individuals, and can effect damping or recruitment—that is, 'on or off' responses. It is possible that factors such as these may explain in part the marked variation between individuals in final scar size, the close symmetry between eyes, and the bimodal distribution of scar sizes found in this study.

We considered whether our results could have been the result of biased case collection. We included all sequential patients who fulfilled the entry criteria, but the high mortality in this age group meant that a number of patients could not be included owing to inadequate follow-up. However, we found no obvious differences in the initial photographs of those patients with inadequate follow-up compared with those entered in this study. It is possible that the high peak in the group with large scars may represent patients with severe disease who attend frequently for visual aid; however, we found no difference in follow-up between the small scar and large scar groups.

In summary, we have found that eyes with a large macular scar resulting from age-related SRNVM formation have a high probability of developing a large scar if SRNVM forms in the remaining eye. This has implications for the management of patients and for the design of clinical trials.

We are grateful to Professor Alan Bird for his helpful comments and advice.

- Ghahour M, Allan D, Foulds WS. Common causes of blindness and visual handicap in the West of Scotland. *Br J Ophthalmol* 1983; 67: 209–13.
- Hyman LG, Lillienfeld AM, Ferris FL III, Fine SL. Senile macular degeneration: a case-control study. *Am J Epidemiol* 1983; 118: 213–27.
- Nasrallah FP, Jalkh AE, Friedman GR, Trempe CL, McMeel JW, Schepens CL. Visual results with low-vision aids in age-related macular degeneration. *Am J Ophthalmol* 1988; 106: 730–4.
- Weiter JJ, Wing GL, Trempe CL, Mainster MA. Visual acuity related to retinal distance from the fovea in macular disease. *Ann Ophthalmol* 1984; 16: 174–6.
- Gregor Z, Bird AC, Chisholm IH. Senile disciform macular degeneration in the second eye. *Br J Ophthalmol* 1977; 61: 141–7.
- Leibowitz H, Krueger DE, Maunier LR. The Framingham Eye Study Monograph: an ophthalmological and epidemiological study of cataract, glaucoma, diabetic retinopathy, macular degeneration. *Surv Ophthalmol* 1980; 24: 335–610.
- Coffey AJH, Brownstein S. The prevalence of macular drusen in postmortem eyes. *Am J Ophthalmol* 1986; 102: 164–71.
- Chuang EL, Bird AC. Bilaterality of tears of the retinal pigment epithelium. *Br J Ophthalmol* 1988; 72: 918–20.
- Berkow JW. Subretinal neovascularization in senile macular degeneration. *Am J Ophthalmol* 1984; 97: 143–7.
- Grey RHB, Bird AC, Chisholm IH. Senile disciform macular degeneration: features indicating suitability for photocoagulation. *Br J Ophthalmol* 1979; 63: 85–9.
- Folk JC. Aging macular degeneration: clinical features of treatable disease. *Ophthalmology* 1985; 92: 594–602.
- Bressler SB, Bressler NM, Fine SL, McCormick P, Auer C. Subfoveal neovascular membranes in senile macular degeneration: relationship between membrane size and visual prognosis. *Retina* 1983; 3: 7–11.
- Guyton DR, Fine SL, Maguire MG, Hawkins BS, Owens SL, Murphy RP. Subfoveal choroidal neovascular membranes in age-related macular degeneration: visual prognosis in eyes with relatively good initial visual acuity. *Arch Ophthalmol* 1986; 104: 702–5.
- Melrose MA, Magargal LE, Donoso LA, Goldberg RE, Edmonds SE. Vision parameters in krypton and laser photocoagulation of subfoveal neovascular membranes. *Ophthalmic Surg* 1985; 16: 495–502.
- Fleiss JL. *Statistical methods for rates and proportions*. 2nd ed. New York: Wiley, 1981.
- Landis RJ, Koch GG. The measurement for observer agreement for categorical data. *Biometrics* 1977; 33: 159–74.
- Melrose MA, Magargal LE, Lucier AC. Identical twins with subretinal neovascularization in complicating senile macular degeneration. *Ophthalmic Surg* 1985; 16: 648–51.
- Newsome DA, Swartz M, Leone NC, Hewitt AT, Wolford F, Miller ED. Macular degeneration and elevated serum ceruloplasmin. *Invest Ophthalmol Vis Sci* 1986; 27: 1675–80.
- Hoshino M, Mizuno K, Ichikawa H. Aging alterations of retina and choroid of Japanese: light microscopic study of macular region of 176 eyes. *Jpn J Ophthalmol* 1984; 28: 89–102.
- Gregor ZJ, Joffe L. Senile macular changes in the black African. *Br J Ophthalmol* 1978; 62: 547–50.
- Blumenkranz MS, Russell SR, Robey MG, Kott-Blumenkranz R, Penneys N. Risk factors in age related maculopathy complicated by choroidal neovascularization. *Ophthalmology* 1986; 93: 552–7.
- Bressler NM, Bressler SB, Gragoudas ES. Clinical characteristics of drusen in patients with exudative versus non-exudative age-related macular degeneration. *Retina* 1988; 8: 109–14.
- Smiddy WE, Fine SL. Prognosis of patients with bilateral macular drusen. *Ophthalmology* 1984; 91: 271–7.
- Miller H, Miller B, Ryan SJ. The role of retinal pigment epithelium in the involution of subretinal neovascularization. *Invest Ophthalmol Vis Sci* 1986; 27: 1644–52.
- Teeters VW, Bird AC. The development of neovascularization of senile disciform macular degeneration. *Am J Ophthalmol* 1973; 76: 1–18.
- Klein ML, Jorizzo PA, Watzke RC. Growth features of choroidal neovascular membranes in age-related macular degeneration. *Ophthalmology* 1989; 96: 1416–21.
- Strahlman ER, Fine SL, Hillis A. The second eye of patients with senile macular degeneration. *Arch Ophthalmol* 1983; 101: 1191–3.
- Glaser BM, Campochiaro PA, Davis JL Jr, Jordan JA. Retinal pigment epithelial cells release inhibitors of neovascularization. *Ophthalmology* 1987; 94: 780–4.
- Penfold PL, Killingsworth MC, Sarks SH. Senile macular degeneration. The involvement of giant cells in atrophy of the retinal pigment epithelium. *Invest Ophthalmol Vis Sci* 1986; 27: 364–71.
- Penfold PL, Provis JM, Billson FA. Age-related macular degeneration: ultrastructural studies of the relationship of leucocytes to angiogenesis. *Graefes Arch Clin Exp Ophthalmol* 1987; 225: 70–6.

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ADVERSE

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PRODUCT LICENCE HOLDER AND NUMBER: Alcon Laboratories U.K. 0649/0097

DATE OF PREPARATION: SEPTEMBER

REFERENCES: 1 Jones FL, Ekberg NL. [Letter N. Eng.] Med 1979; **301**: 270.

2 Levy NS, Boone L, Ellis E. Glaucoma 1985; **7**: 54-62.

3 Schaefer RB, Abuan T, Ward R L, Beasley CH. Am J Ophthalmol 1984; **97**: 86-92.

4 Van Buskirk EM. New Trends in Ophthalmol 1986; **104**: 1178-1184.

Further information is available on request

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Traumatic hyphaema: a retrospective study of 314 cases

Patrick Kearns

Abstract

A retrospective study was made of 314 consecutive cases of traumatic hyphaema in a mixed urban and rural Scottish population. Secondary haemorrhage occurred in 4.1% of cases and was not associated with a worsening of final visual acuity. There were no identifiable risk factors for secondary haemorrhage. Poor visual outcome was in most cases attributable to retinal pathology. The use of antifibrinolytic agents does not appear to be necessary in such a population, and the importance of detecting associated retinal detachment is emphasised.

Traumatic hyphaema is regarded as a sign of ocular trauma requiring, in most centres, admission to hospital. It is almost invariably associated with damage to the anterior segment and frequently to the posterior segment.¹⁻⁵ Hospital treatment aims at promoting resolution of the anterior chamber clot, prevention of further haemorrhage and associated complications, and identification and treatment of any posterior segment injuries.

Secondary haemorrhage has come to be considered the single most important complication of traumatic hyphaema, and in recent years a wealth of literature from North America and Scandinavia has been produced as attempts have been made to prevent its occurrence.⁶⁻¹³ As a result of this work antifibrinolytic agents have been found effective in reducing secondary haemorrhage and are now widely used as prophylactic treatment.

It has not been the policy in our unit to use antifibrinolytic agents on patients with traumatic hyphaema. Our impression has been that rebleeding is an infrequent occurrence and that when it does occur it is not associated with a significant deterioration in visual prognosis. Furthermore we have tended to regard posterior segment damage as the most important consideration in these patients.

To establish whether these impressions were correct the following retrospective study was performed.

Material and methods

The Princess Alexandra Eye Pavilion receives the majority of emergency ophthalmology referrals from Lothian Region, population approximately 750 000. Our policy is to admit all patients with traumatic hyphaema and, where possible, prescribe bed rest for several days until most of the hyphaema has resolved. However, children are rarely, if ever, maintained on strict bed rest; the most that can be achieved is preventing excessive exertion and further possible eye trauma. Furthermore, many adult patients are mobilised as early as the second day after injury, and so bed rest is not applied rigidly during the danger period for rebleeding.

Although patients with microscopic hyphaema are not routinely admitted, some are admitted at the discretion of the examining doctor, and therefore a number were included in the study.

During the period 1 March 1981 to 29 February 1988, 375 patients were admitted with traumatic hyphaema. The case records of 334 (89%) of these patients were available for review.

Twenty (6%) of the 334 were excluded on the grounds that they did not fulfil the criteria of hyphaema secondary to blunt trauma (for example, post-operative, following penetrating injury, or secondary to rubeosis iridis or other pathology) leaving a total of 314 cases.

The following information was extracted from the notes; name, date of birth, age, sex, date of injury, date of admission and medical history, mechanisms of injury, visual acuity, size of hyphaema, intraocular pressure, abrasion and other ocular injuries, funduscopy findings, complications, duration of hyphaema, length of stay in hospital, gonioscopy findings, final visual acuity, and length of follow-up.

For the purposes of the study the size of the hyphaema was classified as follows: grade 1, those filling up to 25% of the anterior chamber; grade 2, up to 50%, grade 3, up to 75%; grade 4, 75% and over.

Results

Data were collected over a seven-year period on a total of 314 patients. The annual incidences are shown in Figure 1. Distribution according to age showed a peak incidence among those aged 10-19 years (Fig 2); 78% of all patients were under 30 years of age. There was a marked preponderance of males (male:female ratio 5.4:1). The mean follow-up period was five months.

Mechanisms of injury are summarised in

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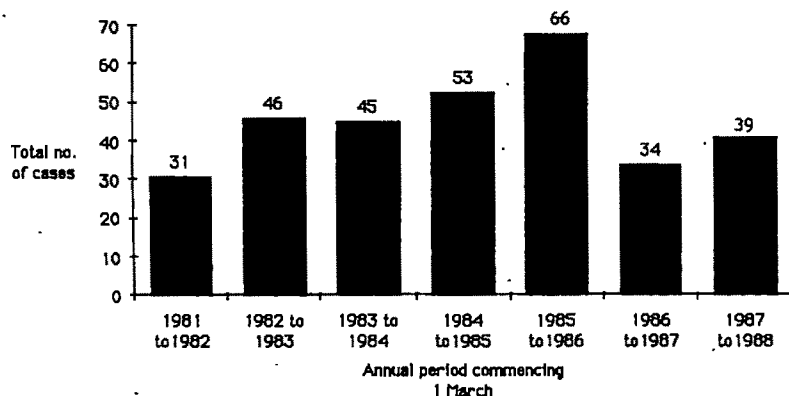


Figure 1 Annual incidence of traumatic hyphaema.

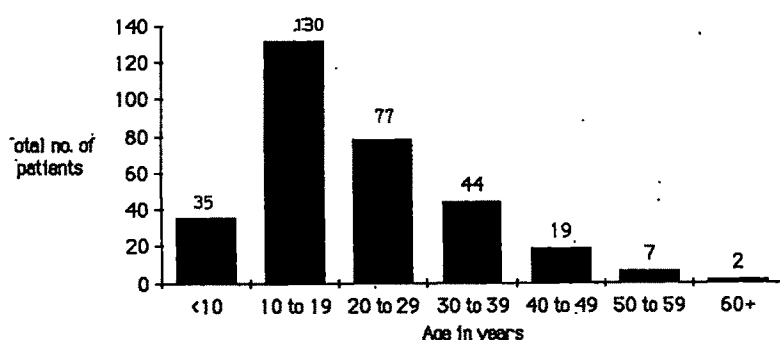


Figure 2 Age distribution of patients with traumatic hyphaema.

Table 1. Sporting injuries accounted for 39.2% of all cases, criminal assault 20.7%, accidents in the home, 17.8%, and accidents at work 9.9%.

Various associated injuries and complications are listed in Table 2. Traumatic mydriasis was the commonest feature, present in 55.7% of cases. Intraocular pressure was raised (above 25 mmHg) in 22% of patients at presentation. In all but three cases the intraocular pressure was normal by the time of discharge. Of the three exceptions two required anterior chamber wash-out for 'blackball hyphaema', and the third had a more prolonged duration of raised pressure, requiring continued β blocker treatment. This patient was lost to follow-up after only two months and had only minimal angle recession on gonioscopy.

Gonioscopy was performed so infrequently that no conclusion could be reached as to the prevalence of angle recession. However, of the 20 eyes examined 15 had some degree of angle recession. The size of hyphaema at presentation is shown in Table 3. The table also shows the incidence of rebleeding, associated with each grade of initial hyphaema. The numbers of grades 3 and 4 hyphaema are too small, as are the rebleed rates, to show any statistically significant association between size and risk of secondary haemorrhage.

Thirteen patients (4.1%) suffered secondary haemorrhage in hospital. No factor studied was associated with an increased risk of rebleeding, including age, sex, mechanism, of injury, or grade of initial hyphaema. In all cases rebleeding occurred between two and four days after the injury. The secondary bleed was small in 11 cases. In two cases the anterior chamber became entirely filled with blood. However, all cases resolved with further bed rest, and only one of the patients with the total hyphaema required acetazolamide for control of raised intraocular pressure. The final visual acuity was 6/9 or better in all but one case, in which vision was reduced owing to macular scarring.

A further seven patients presented with apparent secondary haemorrhage – a history of sudden pain and reduction in vision occurring two to four days after blunt trauma to the eye. All patients in this group regained 6/12 vision or better. Both patients who required anterior chamber washouts were in this group.

Only 3 patients were observed who developed glaucoma as a delayed or late complication. One of these, discussed above, was lost to follow-up. Of the remaining two, one was a young woman who sustained an initially large hyphaema which

Table 1 Mechanism of injury

Mechanism of injury	No	%
Accident in the home	56	17.8
Accident at work	31	9.9
Sport		
Football	45	14.3
Squash	31	9.9
Badminton	16	5.1
Tennis	10	3.2
Golf	7	2.3
Hockey	4	1.3
Rugby	4	1.3
Volleyball	2	0.6
Cricket	1	0.3
Martial Arts	1	0.3
Other Sports	2	0.6
Total	123	39.2
Assault		
Missile	34	10.8
Other	31	9.9
Total	65	20.7
Play*	32	10.2
Unspecified	7	2.2

*Group of children: injury occurred during unsupervised play; exact mechanism of injury unclear.

Table 2 Complications of blunt trauma associated with hyphaema

Complications	No	%
Immediate		
Traumatic mydriasis	175	55.7
Corneal abrasion	132	42
Comotio	36	11.5
Lid laceration	23	7.3
Vitreous haemorrhage	15	4.8
Choroidal rupture	14	4.5
Rebleed	13	4.1
Fracture	8	2.5
Iridodialysis	11	3.5
Retinal haemorrhage	9	2.9
Corneal laceration	3	1
Dislocated lens	3	1
Retinal tear	2	0.6
Retinal detachment	1	0.3
Optic nerve damage	1	0.3
Delayed/late		
Cataract	15	5.1
Recurrent iritis	7	2.2
Glaucoma	3	1
Late retinal detachment	3	1
Macular scar	3	1
Corneal staining	1	0.3

Table 3 Size of hyphaema and incidence of rebleed

Grade	No of cases	No of rebleeds	%
1	244	10	4
2	47	2	4
3	9	1	11
4	8	0	0
Total		13	

settled with conservative management, but she was readmitted eight days after the initial injury because of an acute 'ghost cell' glaucoma. This again settled with conservative management. The final patient suffered angle recession of greater than 180° and required trabeculectomy six months after the injury to control the intraocular pressure.

Sixteen patients developed lens opacities, though the exact nature and extent was rarely recorded. Three patients required lens extraction; one required extracapsular extraction and vitrectomy for a dense cataract with associated vitreous haemorrhage (Table 4, patient 1). A second had lensectomy following anterior chamber washout of a 'blackball' hyphaema, and a third had lensectomy and anterior vitrectomy for a dislocated lens.

Details of patients requiring retinal detachment surgery or prophylaxis for retinal breaks are given in Table 4. Of 15 patients who suffered a

Table 4 Details of patients requiring retinal surgery

Patient	Retinal Injury (Visual acuity at initial examination following injury)	Location	Period between injury and diagnosing of retinal injury	Treatment	Final visual acuity	Other features
1	Retinal tear (PL)	Superonasal	>One week	Vitrectomy and endolaser	HM	Orbital FB removed. Macular choroidal rupture. Vitrectomy and endolaser combined with extra-capsular lens extraction (cataract)
2	Retinal horseshoe tear with traction (6/6)	Superotemporal	3 weeks	Cryopexy and encircling band	6/9	
3	Disinsertion (6/5)	Inferotemporal	4 weeks	Cryopexy and encircling band	6/6	
4	Tractional detachment: no tear/hole found (6/9)		11 months	Cryopexy and encircling band	6/24	
5	Disinsertion (6/9)	Superotemporal	3 months	Cryopexy and encircling band	6/60	Had complained of field defect from time of injury
6	Disinsertion (CF)	Superotemporal	Immediate	Cryopexy and encircling band	6/60	Amblyopic eye

CF=counting fingers. PL=perception of light. FB=foreign body.

vitreous haemorrhage only one was found to have an underlying retinal tear. This patient required vitrectomy and endolaser treatment to the tear. One other patient developed gradual condensation of vitreous haemorrhage with tractional retinal detachment (Table 4 patient 4).

Comotio retinae was present in 36 patients – peripherally in 29 cases, at the macula in 7. Three of these developed macular scars.

Five patients suffered blow-out orbital fractures, three others suffering malar and other orbital rim fractures.

Corneal blood staining occurred in only one patient, who presented with a total hyphaema due to secondary haemorrhage. Final visual acuity was 6/12, following anterior chamber washout.

Although the hospital policy was to give no topical treatment unless specifically indicated, 64 patients received topical steroids, nine ocular hypotensive treatment, and 13 both during their stay. Surgical intervention for associated problems was uncommon: one trabeculectomy, two lens extractions, five retinal procedure, and two anterior chamber washouts. Choroidal rupture, occurring in 4.5% of patients, was the single most frequent cause of reduced vision. The mean duration to resolution of hyphaemas was 2.6 days (range 1–10), and the mean hospital stay was 4.8 days (range 1–15).

Table 5 shows the visual acuity, with the cause of reduced vision, for those patients with a final vision worse than 6/12.

General medical and drug histories were unremarkable except in the single case of a child with acute lymphatic leukaemia. Patients had not been questioned about the use of aspirin.

Discussion

The data gathered from our series of 314 patients are generally in keeping with those of major studies previously reported^{1–5 & 14–19} with regard to age and sex distribution, mechanism of injury, frequency of associated ocular trauma, and size of hyphaema. The annual incidence was fairly constant, and the patients were predominantly young and male. In recent years sporting injuries have become a major cause while accidents at work have become relatively less frequent.^{20,21} In our series sport related injuries are four times commoner than work related injuries. Football, squash, and badminton appear to be the most dangerous.

The pattern of anterior segment damage was in keeping with that of previous series.²² After corneal abrasion, traumatic mydriasis was the most common abnormality found at initial examination. Although gonioscopy was carried out only on a minority of patients, it is known that some degree of angle recession occurs in the great majority of eyes sustaining hyphaema as a result of blunt trauma.²³ However, it is also recognised that glaucoma secondary to angle recession is rare and occurs only when recession is present over more than 240° of the angle.^{22–24}

Table 5 Causes of reduction in visual acuity

Final visual acuity	No of patients	Patient	Cause of decreased visual acuity
PL	1	1	Previous poor VA: Fuchs's heterochromic iridocyclitis with cataract
HM	3	1	Initial post-traumatic VA was HM: nil found. Amblyopia
		2	Choroidal rupture: required vitrectomy, endolaser and cataract extract
		3	Table 4, patient 1
CF	2	1	Macular scar following commotio
		2	Choroidal rupture
6/60	2	1	Choroidal rupture
		2	Retinal detachment
6/36	2	1	Retinal detachment
		2	Cataract
6/24	3	1	Patient had rebled. No obvious cause of decreased visual acuity. Acuity prior to rebled not recorded
		2	No cause found
		3	No cause found
6/18	3	1	Retinal detachment and choroidal rupture
		2	Comotio at macula; residual scarring
		3	Cataract
		3	No cause found

CF=counting fingers. HM=hand movement. PL=perception of light.

That such secondary glaucoma is rare seems to be confirmed by our finding of only one such case in our series.

The incidence of secondary haemorrhage in hospital (4.1%) is in keeping with rates found in a larger number of European studies^{6-8 17-19} of patients treated conservatively (5-10%). These figures are considerably lower than those found in most of the American series (16-38%).^{1 2 9-11 16 25} This discrepancy has been recognised for some time, though no convincing explanation has been found. It has been noticed that rebleed rates were higher in populations with larger proportions of black patients.²⁶ In North American series in which the ethnic distribution is similar to Northern European studies the rebleed rates have been close to European rates.^{4 12} This discrepancy remains unresolved and is likely to remain so until a large controlled study taking account of ethnic variation is performed.

Various treatments to reduce the incidence of rebleeding have been assessed: bed rest, patching of one or both eyes, miotics,³ mydriatics,¹⁸ steroids,^{3 18 27 28} and antifibrinolytic agents. Vitamins C and K and even snake venom have been advocated.¹ However, only antifibrinolytic agents have been shown by randomised, prospective studies to be effective in both Europe and North America,^{6-8 9-11 13} though several recent studies have shown no benefit.^{15 29} Even in European studies where rebleed rates are low in placebo and conservatively treated groups antifibrinolytics have been shown to reduce the incidence further. Aminocaproic acid (100 mg/kg four times a day for five days) has become the treatment of choice for traumatic hyphaema in North America and tranexamic acid (25 mg/kg three times a day for five days) in Europe. Side effects such as nausea, vomiting, and hypotension occur in up to 50% of patients taking aminocaproic acid;²⁹ the incidence and severity of side-effects are said to be much lower with tranexamic acid. Although it is considered that full mobilisation is allowed when patients are 'protected' by antifibrinolytics, it must be pointed out that the efficacy of bed rest has never been demonstrated in a controlled study.^{2 4}

The high incidence of side effects means the use of these drugs can be justified only if a clear benefit can be demonstrated. Although antifibrinolytics do seem to reduce the rebleeding rate, the question must also be asked: does rebleeding have significant consequences? The evidence is conflicting, reports ranging from a dramatic worsening of visual prognosis when rebleeding occurs, especially if the rebleed is prolonged and is accompanied by a marked rise in intraocular pressure,^{13 17 30} to no difference in prognosis.^{11 15 16 25} It has been suggested that it is the size of the hyphaema rather than its primary or secondary nature that correlates with prognosis. Hence the finding that prognosis is poorer with secondary haemorrhage could be explained by secondary haemorrhages tending to be larger than primary ones.^{2 4} However, this would only apply if large hyphaemas and raised intraocular pressure were the principal cause of poor vision. Studies have repeatedly shown that it is not the number of rebleeds that determine the overall visual outcome but the frequency of associated

ocular injuries, in particular posterior segment injuries. In our study rebleeding was not associated with a worsening of visual prognosis, even in those patients who presented late with 'black ball' secondary bleeds and who required anterior chamber washouts. In terms of final visual acuity the use of antifibrinolytics would therefore not have benefited any of our patients who subsequently rebled.

The posterior pole complication most frequently responsible for poor visual acuity was choroidal rupture (Table 5). Retinal tears and/or detachment appear to occur with some frequency, and are a preventable cause of visual loss. Table 4 shows that the presence of a tear or detachment is not always immediately obvious, perhaps because in some cases the detachment takes some time to develop. However, retinal tears or holes occur at the time of injury³¹ and will be missed unless looked for. Although retinal detachment may occur many years after trauma, 80% will occur within two years, almost invariably owing to peripheral retinal damage sustained at the time of injury.³² Our findings of a predominance of oral disinsertions is in keeping with Cox and colleagues' classic description of detachment in ocular trauma,³² though in our series most were superotemporal rather than superonasal.

Hyphaema, therefore, is just one feature of a constellation of ocular injuries that follow blunt trauma. In a predominantly Caucasian Northern European population such as ours secondary rebleed is uncommon and is not associated with a worsening of visual prognosis. There were no features which allowed identification of those at risk of rebleeding in our study. Corneal blood staining sufficient to cause impairment of vision was not seen. Poor visual acuity was in general due to posterior segment damage, the diagnosis of which was often delayed. Secondary glaucoma was found to be a rare complication. Our conservative approach to traumatic hyphaema therefore seems justified.

While the overwhelming concern with hyphaema and secondary haemorrhage is understandable (certainly in those American centres with large numbers of black patients, in whom rebleeding seems to be more common²⁶) there is a danger of neglecting other important aspects of blunt ocular trauma. Posterior segment damage can occur without an associated hyphaema.⁵ Efforts should be made to detect and treat retinal breaks, dialyses, or holes which may not be obvious until full examination with the binocular indirect ophthalmoscope and scleral indentation have been carried out. Gonioscopy should be performed at some stage in the follow-up period (once is enough, as angle recession is constant once present²⁴) to detect eyes with 180° or more recession, bearing in mind that even within this group only a minority will develop glaucoma.^{23 24}

Although it is our policy to admit all patients presenting with traumatic hyphaema our finding of a group of patients presenting with secondary haemorrhage suggests that a number of patients sustaining hyphaema never attend hospital. The visual outcome in these patients was in fact very good. Since bed rest, our only consistent treatment, is of doubtful benefit, a case could be made

for allowing patients who present with hyphaema to go home with instructions to minimise physical activity and to return promptly should they develop symptoms of a rebleed. The patient could be discharged from review as soon as the examiner was satisfied that he had adequately examined the peripheral retina, and that gonioscopy had ruled out excessive angle recession.

- 1 Thygeson P, Beard C. Observations on traumatic hyphema. *Am J Ophthalmol* 1952; 35: 977-85.
- 2 Edwards WC, Layden WE. Traumatic hyphema: a report of 184 consecutive cases. *Am J Ophthalmol* 1973; 75: 110-6.
- 3 Rakusin W. Traumatic hyphema. *Am J Ophthalmol* 1972; 74: 284-92.
- 4 Wilson FM. Traumatic hyphema, pathogenesis and management. *Ophthalmology* 1980; 87: 910-9.
- 5 Eagling EM. Ocular damage after blunt trauma to the eye; its relationship to the nature of the injury. *Br J Ophthalmol* 1974; 58: 126-40.
- 6 Bramsen T. Traumatic hyphaema treated with the antifibrinolytic drug tranexamic acid. *Acta Ophthalmol (Kbh)* 1976; 54: 250-6.
- 7 Varnek L, Dalsgaard C, Hansen A, Klie F. The effect of tranexamic acid on secondary haemorrhage after traumatic hyphaema. *Acta Ophthalmol (Kbh)* 1980; 58: 787-93.
- 8 Uusitalo RJ, Ramta-Kemppainen L, Tarkkanen A. Management of traumatic hyphema in children; an analysis of 340 cases. *Arch Ophthalmol* 1988; 106: 1207-9.
- 9 Crouch ER, Frenkel M. Aminocaproic acid in the treatment of traumatic hyphema. *Am J Ophthalmol* 1976; 81: 355-60.
- 10 McGettrick JJ, Jampol LM, Goldberg MF, Frenkel M, Fiscella RG. Aminocaproic acid decreases secondary haemorrhage after traumatic hyphema. *Arch Ophthalmol* 1983; 101: 1031-3.
- 11 Kunter B, Fourman S, Brein K, Hobson S, et al. Aminocaproic acid reduces the risk of secondary haemorrhage in patients with traumatic hyphema. *Arch Ophthalmol* 1987; 105: 206-8.
- 12 Wittman EJ. Traumatic hyphema (letter). *Arch Ophthalmol* 1984; 102: 356-7.
- 13 Goldberg MF. Antifibrinolytic agents in the management of traumatic hyphema (editorial). *Arch Ophthalmol* 1983; 101: 1029-30.
- 14 Amoni SS. Traumatic hyphaema in a defined population. *Am J Ophthalmol* 1981; 65: 439-44.
- 15 Kennedy RH, Brubaker RF. Traumatic hyphema in a defined population. *Am J Ophthalmol* 1988; 106: 123-30.
- 16 Thomas MA, Parrish RK, Feuer WJ. Rebleeding after traumatic hyphema. *Arch Ophthalmol* 1986; 104: 206-10.
- 17 Gregerson E. Traumatic hyphaema: a report of 200 successive cases. *Acta Ophthalmol (Kbh)* 1962; 40: 192-9.
- 18 Ohrstrom A. Treatment of traumatic hyphaema with corticosteroids and mydriatics. *Acta Ophthalmol (Kbh)* 1972; 50: 549-55.
- 19 Benersson E, Ehinger B. Treatment of traumatic hyphaema. *Acta Ophthalmol (Kbh)* 1975; 53: 914-23.
- 20 Jones NP. One year of severe eye injuries in sport. *Eye* 1988; 2: 484-7.
- 21 MacEwen CJ. Sport associated eye injury: a casualty department survey. *Br J Ophthalmol* 1987; 71: 701-5.
- 22 Canavan YM, Archer DB. Anterior segment consequences of blunt ocular trauma. *Br J Ophthalmol* 1982; 66: 549-55.
- 23 Tonjum AM. Gonioscopy in traumatic hyphaema. *Acta Ophthalmol (Kbh)* 1966; 44: 650-64.
- 24 Kaufman JH, Tolpin DW. Glaucoma after traumatic angle recession. *Am J Ophthalmol* 1974; 78: 648-54.
- 25 Spaeth GL, Levy PM. Traumatic hyphema: its clinical characteristics and the failure of estrogens to alter its course. *Am J Ophthalmol* 1966; 62: 1098-106.
- 26 Spoor TC, Kwitko EM, O'Grady JM, Ramocki JM. Traumatic hyphema in an urban population. *Am J Ophthalmol* 1990; 109: 23-7.
- 27 Spoor TC, Hammer M, Belloso H. Traumatic hyphema: failure of steroids to alter its course; a double blind prospective study. *Arch Ophthalmol* 1980; 98: 116-9.
- 28 Rynne MV, Romano PE. Systemic steroids in the treatment of traumatic hyphema. *J Pediatr Ophthalmol Strab issues* 1980; 17: 141-3.
- 29 Kraft SP, Christianson MD, Crawford JS, Wagman RD, Antoszyk JH. Traumatic hyphema in children: treatment with epsilon-aminocaproic acid. *Ophthalmology* 1987; 94: 1232-7.
- 30 Agapitos PJ, Leon-Paul N, Clarke WN. Traumatic hyphema in children. *Ophthalmology* 1987; 94: 1238-41.
- 31 Cooling RJ. Ocular injuries. In: Miller SJH ed. *Clinical ophthalmology*. Bristol: Wright, 1987: 366.
- 32 Cox MS, Schepens CL, Freeman HM. Retinal detachment due to ocular contusion. *Arch Ophthalmol* 1966; 76: 678-85.

Penetrating keratoplasty for keratoconus: complications and long-term success

K W Sharif, T A Casey

Abstract

A series of 100 penetrating keratoplasties for keratoconus performed between 1968 and 1986 were reviewed for long-term results. The mean follow-up was 6.1 years with a range of 4-16 years. The systemic associations and the post-operative complications were analysed. Grafting in cases associated with Down's syndrome had a higher incidence of complications. 93% of grafts remained clear and 81% achieved a final corrected visual acuity of 6/12 or better. 21% of eyes developed a homograft reaction, with 50% of rejection episodes occurring in the first year after operation. Factors associated with higher incidence of rejection included loose sutures, traumatic wound dehiscence, and grafts larger than 8.5 mm. Only three grafts with rejection episodes lost graft clarity, while rejection in the rest was successfully reversed with topical steroid therapy. No relationship was found between donor age and long-term graft clarity.

Keratoconus patients have one of the highest success rates of any group of patients undergoing penetrating keratoplasty. Since Castroviejo reported successful grafting for keratoconus in 1927, many reports have confirmed a favourable prognosis.¹⁻⁴ Many of the published reports, however, had a limited follow-up time, and the life span of some corneal grafts has been questioned after specular microscopic studies that showed a continuous decline in the endothelial cell count after keratoplasty.⁵

Although graft clarity can be expected in more than 90% of cases, postoperative complications in the form of high astigmatism, posterior subcapsular cataract, and secondary glaucoma can lead to a less than perfect visual outcome.

The aim of our study was to select a group of keratoconus patients previously unoperated upon and determine the long-term graft clarity, the relationship of the donor age to graft clarity, the incidence of operative and postoperative complications, including homograft rejection, and finally to determine the probability of graft survival in the group of patients who developed one or more rejection episodes during the follow-up period.

Materials and methods

The subjects of the present study were keratoconus patients who underwent penetrating keratoplasty over an 18-year period at the Corneo-Plastic Unit, Queen Victoria Hospital. All the patients undergoing this procedure were included provided they had had no previous intraocular surgery and had a four-year minimum

follow-up time. One hundred penetrating keratoplasties met these criteria. The case notes were reviewed, and follow-up information was sought from the referring ophthalmologist in nine cases that had not been evaluated in our clinic during the past two years. Some of these patients selected for our study had regrafts or other surgical procedures after the initial keratoplasty. However, our graft success results relate to the original keratoplasty.

Despite the fact that in most cases when a failure occurred a subsequent graft was successfully performed, we have included these cases in our statistics as 'failed grafts', since our aim was to define the prognosis of the initial surgery.

All the patients in our series were selected for surgery if they could not obtain industrially useful vision ($<6/18$) with contact lenses or spectacles, or if they could obtain improved vision with contact lenses but only for limited periods of time. Donor tissues was obtained from whole globes stored at 4°C for up to 24 hours with the grafts performed before 1984 (86 grafts). Corneae stored in McCarey-Kaufman medium and chondroitin sulphate dextran (K-sol) were used in the subsequent 14 grafts (1984-6).

Penetrating keratoplasties in our series were performed according to the method in use during that time interval, and the numbers per period are indicated in Table 1. All the operations were performed under general anaesthesia by the senior author of this report (TAC) and the fellows of the Corneal Unit. Owing to the change in the method of tissue storage since 1984 all the donor corneae were trephined from the endothelial side by a punch trephine. Before 1975 grafts were sutured with interrupted 8-0 virgin silk (29 cases). From 1975 10-0 nylon sutures (interrupted and continuous) were used instead (71 cases). At the conclusion of surgery dexamethasone 4 mg and gentamicin 20 mg were injected subconjunctivally and Chloramphenicol 1% eyedrops were instilled. Postoperatively Chloramphenicol 1% eyedrops and dexamethasone 0.1% eyedrops were used routinely four times a day for one month, after which they were tapered off gradually.

The results reported were based on the appearance of the graft at the last clinical examination and the patient's visual acuity. At the same time the hospital notes were reviewed to determine any interim postoperative compli-

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Table 1 Surgical techniques

Date	Donor trephine	Suture type	Number of grafts
1968-75	Epithelial side	8-0 silk	29
1975-84	Epithelial side	10-0 nylon	57
1984-6	Endothelial side	10-0 nylon	14

cations. Grafts with total or partial oedema were counted as failed or failing.

Graft rejection was diagnosed by the appearance in a previously clear graft of at least one of the following: (1) endothelial rejection line; (2) keratic precipitates; or (3) localised graft oedema, the edge of which usually coincided with the keratic precipitates.

Graft survival has been expressed graphically by Kaplan and Meier survival curves, which take account of staggered recruitment and variable follow-up such that many grafts remained clear at final review and were denoted censored data. They were censored because eventual failure cannot be excluded, but the event has not been observed.

When a rejection was diagnosed, the therapy consisted of topical steroids ever two hours and topical prophylactic antibiotics four times a day along with subconjunctival dexamethasone injections according to the patient's response.

Results

One hundred penetrating keratoplasties for keratoconus have been examined retrospectively. The grafts in our series had an average follow-up of 6.1 years with a range of 4–16 years. The following indices were recorded:

1. *Age and sex.* Patients ranged in the age at the time of diagnosis from six to 48 years, mean 9.2 years. Age at the time of penetrating keratoplasty ranged from 11 to 51 years, mean 27.9 years. There were 68 males and 32 females in our series (2:1 ratio).

2. *Systemic and ocular associations.* The various associations of keratoconus in our patients are listed in Table 2; manifestations of atopy were the most common. Keratoplasties were performed in four cases of Down's syndrome when advanced keratoconus had led to repeated attacks of acute hydrops.

3. *Early and late complications.* Herniation of the iris-lens diaphragm occurred during 10% of the keratoplasties (Fig 1), but this was treated easily at the time with no effect on the final outcome. One patient had a 2 mm hyphaema following a peripheral iridectomy, which resolved spontaneously by the fourth postoperative day.

The parietic pupil, resulting from iris sphincter paralysis, occurred in 4% of the cases. In all of these cases a fixed dilated pupil was noted on the first postoperative day and it remained dilated over the follow-up period (Fig 2). All these cases were given Pilocarpine 2% eyedrops in four doses one hour preoperatively with no mydriatics instilled postoperatively. None of these cases had a wound leak with flat anterior chamber, and



Figure 1 Bulging of the iris-lens diaphragm following host corneal trephination.

there were no anterior synechiae. Only one patient had associated secondary glaucoma. After the routine use of intravenous mannitol preoperatively in 1976 only one case of a parietic pupil was reported in the subsequent 68 grafts.

Cataract. Posterior subcapsular cataract developed in 12% of our cases. The clinical onset varied from 9 months to three years postoperatively (average 18 months). The onset and progression of these cataracts were directly related to the duration of topical steroid therapy. This is clearly demonstrated by the fact that 58% of the patients who developed cataract had previously been treated for one or more rejection episodes, calling for more intensive and prolonged topical steroid therapy than the routine postoperative regimen. Cataract extraction, however, was indicated in only 5% of the patients in our series, – that is 41.6% of those who developed cataracts.

Secondary glaucoma. This occurred in 4% of our cases. One of them was successfully treated by topical therapy, while the remaining three required surgical management. The cases requiring surgery to control the raised pressure all had previous history of rejection episodes involving prolonged topical steroid therapy.

Keratitis. Three cases in our series developed infective keratitis. Two were bacterial keratitis in patients with Down's syndrome, and the third was a fungal keratitis in an immune-compromised eye due to intensive steroid treatment for a rejection episode.

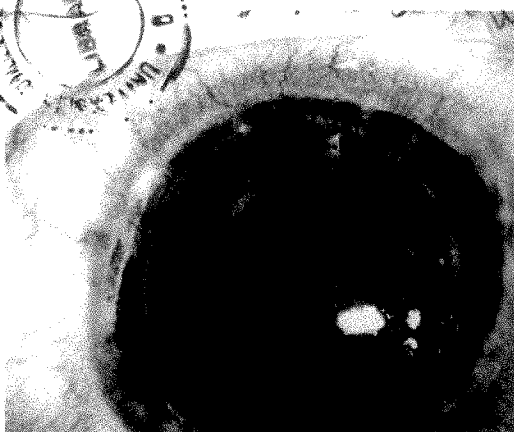


Figure 2 Dilated, fixed pupil following keratoplasty for keratoconus.

Table 2 Systemic and ocular associations

Association	Percentage of cases
<i>I. Systemic</i>	
Hay fever	13
Asthma	8
Eczema	7
Down's syndrome	4
Osteogenesis imperfecta	1
<i>II. Ocular</i>	
Vernal keratoconjunctivitis	2
Retinitis pigmentosa	1

Astigmatism. Astigmatism that could not be successfully neutralised with glasses or contact lenses, following the removal of sutures, occurred in 8% of the cases. All of them were treated with refractive surgery. 5% of the cases had astigmatism with a range of 5.5–8.0 dioptres and a mean value of 6.25 dioptres. This group was treated with relaxing incisions with successful reduction of the astigmatism to a mean value of 2 dioptres, leading to successful visual rehabilitation with glasses. The remaining three cases with high astigmatism, more than 8.5 dioptres, were treated with relaxing incisions at the steepest corneal meridian followed by augmentation sutures placed along the flattest meridian. This method helped to reduce the astigmatism to a mean value of 2.25 dioptres in two cases. The third case had a residual astigmatism of 5.5 dioptres after this method which was treated with wedge resection, leading to successful visual rehabilitation with glasses.

Graft rejection. Homograft rejection occurred in 21% of our cases. Only one of these was an epithelial rejection, which developed seven months postoperatively.

The mean time to the endothelial rejection episodes was 1.8 years, range 17 days to 15 years (Fig 3). Five of these cases had a second rejection episode during the follow-up. Thirteen of the rejection episodes (50%) occurred in the first 12

months. Seven eyes (26.9%) developed a rejection in the second year. Five of the remaining six patients who had a rejection after the second year had had a previous rejection earlier. Factors associated with these rejection episodes included loose sutures in six eyes, one following a traumatic wound dehiscence, and one following treated infective keratitis. The probability of graft survival for all penetrating keratoplasties performed in one series between 1968 and 1986 ($n=100$) was 93% at 2500 days (6.8 years) (Fig 4). Most failures occurred in the first 500 days (1.37 years). The survival curves in (Fig 5) compare the probability of survival between the group of patients with one or more rejection episodes (group A) and those with no history of rejection (group B). It is clearly shown that the probability of survival of group B was 96% at 1000 days (2.7 years), while that of group A was 86% at the same time. We examined the incidence of the graft rejection in relation to the donor size (Table 3). Variation of the graft size between 7 mm and 8.5 mm had no statistically significant effect on the rejection rate. However, 9 mm grafts had a high rejection incidence (50%).

All but three rejection episodes were successfully reversed with topical steroid therapy. The period between the onset of the rejection and the return of the graft varied from 17 days to 140 days, mean 47 days.

4. Long-term graft clarity. 96% of the grafts in our series were clear by the end of the first post-operative year, and 93% were still clear by the end of an average follow-up of 6.1 years. Only seven grafts failed in our series. The cause of failure are listed in Table 4. In a subgroup of ten eyes with an average follow-up of 15 years, 90% of the grafts remained clear.

5. Donor age and graft clarity. Donor age was available for 93 of the 100 grafts (93%). The mean follow-up of these grafts was 8.1 years. The donor age ranged from 13 years to 91 years, mean 65.5 years. Donors were divided into three groups to detect any relationship between long-term graft clarity and donor age, and these groups were: donor age <45, 45–65, and >65 (Table 5). We could not find any statistically

Figure 3 Onset of homograft rejection in relation to postoperative follow-up time.

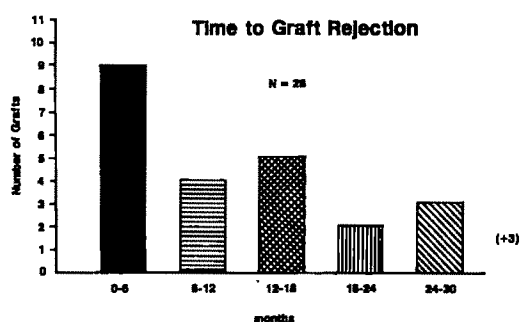


Figure 4 Kaplan-Meier survival curve of all grafts performed between 1968 and 1986 for keratoconus.

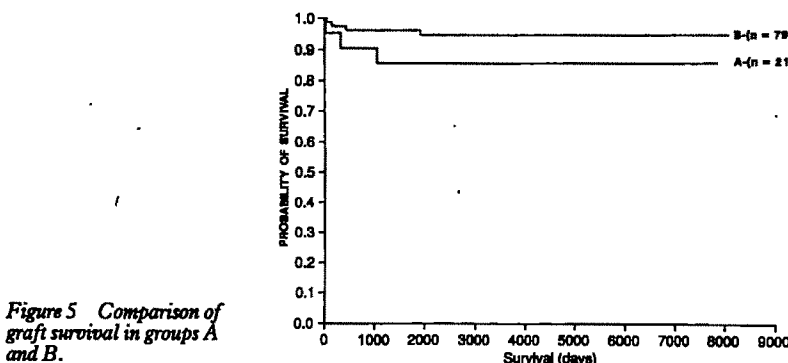
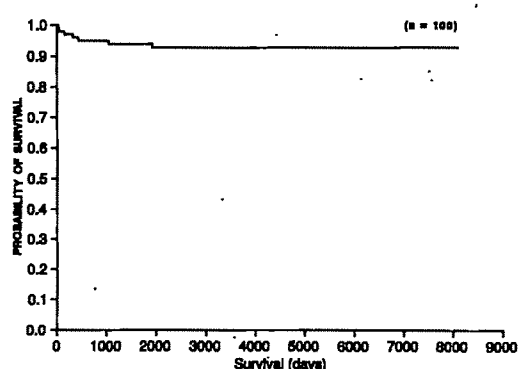


Figure 5 Comparison of graft survival in groups A and B.

Table 3 Rejection incidence in relation to graft size

Size (mm)	Rejection	
	%	Proportion
7.0	16.6	1 of 6
7.5	2.3	3 of 13
8.0	16.6	12 of 72
8.5	25	1 of 4
9.0	50	3 of 6

Table 4 Causes of graft failure

Causes	Number of grafts
Graft rejection	3
Late graft decompensation	2
Infective keratitis	2

Table 5 Donor age and graft clarity (93 grafts)

Donor age	Total number	Clear	Failed
Less than 45 years	7	6	1
45–65 years	34	32	2
More than 65 years	52	49	3

Table 6 Long term visual acuity

Visual acuity	% of eyes
6/9 or better	59
6/12	22
6/18	7
6/24-6/60	8
Less than 6/60	4

Table 7 Causes of visual acuity less than 6/36

Causes	% of eyes
Failed graft	3
Secondary glaucoma	2
Retinal disease	2
Healed infective keratitis	1

significant relationship between long-term graft clarity and donor age ($p=0.38$), which was consistent with previously published reports.⁶

6. Long-term visual outcome. The final corrected visual results of the grafts in our series over an average follow-up of 6.1 years are listed in Table 6. 81% of the eyes achieved visual acuity of 6/12 or better. Residual high astigmatism, decompensation of the graft, and steroid induced cataract were the major cause of decreased acuity. The causes of visual acuity of 6/60 or less are listed in Table 7. The majority of these eyes were successfully regrafted and had a good visual result.

Discussion

Keratoconus is a non-inflammatory axial ectasia of the cornea with an estimated incidence of 1:20 000. It has a slowly progressive course resulting in high degrees of irregular, myopic astigmatism. Although some reports have shown the condition to be predominant in females,⁷ our series had a predominance of males (68%). This is in agreement with reports by Buxton⁸ and Woodward,⁹ who found males to be predominant with proportions of 62% and 60% of their cases respectively.

Various systemic and ocular associations have been found in our case (Table 2). Association with atopy, eczema, and vernal conjunctivitis is important, since these patients may have more immunological problems than expected in non-vascularised corneae.^{10,11} The most advanced cases of keratoconus seen in our series were those associated with Down's syndrome (four cases). The mental retardation of these patients always carries the risk of trauma or infection of an otherwise successful graft. Infective keratitis led to the failure of the initial graft in two of these four cases. The decision to operate on such patients should be based on individual assessment of each case, with particular consideration of the degree of visual impairment, the grade of mental retardation, and the presence or absence of adequate post operative home care and supervision.

The complications following penetrating keratoplasty for keratoconus are relatively few compared with those encountered in grafting high risk patients. The development of a dilated fixed pupil as a complication of grafting in keratoconus has been noted by a number of surgeons including Castroviejo and Paufigue, but it was Urrets-Zavalía¹² who first published

his observations and suggested that the association of fixed dilated pupil, iris atrophy, and secondary glaucoma constituted a specific syndrome which has since been frequently known by his name. In our series 4% of the cases had parietic pupils from the first postoperative day. However, only one developed secondary glaucoma, which confirms previously published reports by Davies and Ruben that glaucoma is not a sequel to the simple parietic pupil.¹³ Glaucoma thus seems to be no more a special complication of keratoplasty in keratoconus than it is of keratoplasty for any other corneal lesion. The parietic pupil can be explained on the basis of ischaemic atrophy of the sphincter pupillae muscle secondary to an iris strangulation phenomenon occurring as a result of anterior displacement of the iris lens diaphragm against the posterior surface and cut edge of the host cornea during surgery. This theory was confirmed in our experience by the fact that, since preoperative intravenous mannitol 20% was used routinely for all grafts performed after 1976, there has been a significant decrease in the incidence of this complication. One case out of 68 grafts had a parietic pupil compared with three out of 32 grafts performed before 1976.

Posterior subcapsular cataract developed in 12% of our patients. However, less than half of these cataracts (41.6%) required extraction. The relation between long-term topical steroid use and the development of cataract and secondary glaucoma was highlighted by the fact that the majority of eyes having these complications in our series were those that required intensive and more prolonged steroid therapy for the treatment of rejection episodes.

There have been variable reports on the incidence of homograft reaction following keratoplasty for keratoconus. Chandler and Kaufmann reported a high incidence of 35% in 1974.¹⁴ A recent report by Trautman and Lambers¹⁵ gave a lower incidence of 11.6%. Our long-term follow-up study (1968-90) showed the incidence to be 21%. The variations of rejection rate among different reports are most probably attributed to the changes in surgical techniques at various times, with the advent of the 10-0 nylon suture closure replacing the previously used virgin silk.

Most of the graft rejections in our study were successfully treated with topical and subconjunctival steroids, and only 3% of the eyes lost graft clarity as a result of endothelial rejection. It was interesting to find that 50% of rejection episodes occurred during the first twelve months post operatively – that is, before suture removal – and that nearly all the eyes that developed a rejection after the second year had a history of an earlier rejection that has been reversed. No significant correlation could be made between the graft size and the risk of rejection when donor size was between 7.0 and 8.5 mm (Table 3). It was interesting, however, to note that larger grafts, namely 9.0 mm, had a higher incidence of rejection reactions (50%). This is probably related to the greater proximity to the limbus and the larger antigenic load.

The long-term results in our series confirm the excellent prognosis found in several previous

reports¹⁵⁻¹⁷ 93% of our cases maintained graft clarity over an average follow-up period of 6.1 years. The excellent rate of graft clarity in the subgroup with a 15-year average follow-up (90%) indicates that the progressive endothelial cell loss reported with specular microscopy over the first year postoperatively⁵ does not forecast ultimate graft failure.

As indicated in Table 6 81% of penetrating keratoplasties provided 6/12 or better vision after 6.1 years average follow-up. 40% of the cases required spectacle correction to achieve this acuity compared with 26% requiring contact lenses and 15% needed no correction.

In summary, penetrating keratoplasty at the present time appears to be the procedure of choice in treating keratoconus, with excellent long-term visual results. The few postoperative complications can be minimised if the patient has been subject to careful follow-up and has been instructed to report immediately if pain, redness, or visual loss develops. The incidence of iatrogenic cataract and secondary glaucoma can be reduced by avoiding the liberal use of topical steroids and by rapidly tapering them off in complicated cases. It is also better to avoid a graft size larger than 8.5 mm, as this carries a higher incidence of rejection reactions.

We thank Mrs Beth Chase-Grey, Mrs Margot Bain, and Mrs Alma Ayles for their great assistance in the preparation of this manuscript. We are grateful to Dr I D Hill for his valuable assistance in the medical statistics of the paper.

- 1 Castroviejo R. Surgery of the Cornea. *Int Abstr Surg* 1937; 65: 489-505.
- 2 Castroviejo R. Keratoplasty in treatment of keratoconus. *Arch Ophthalmol* 1949; 42: 776-800.
- 3 Ehlers N, Olsen T. Long term results of corneal grafting in keratoconus. *Arch Ophthalmol (Kbh)* 1983; 61: 918-26.
- 4 Keates RH, Falkenstein S. Keratoplasty in keratoconus. *Am J Ophthalmol* 1972; 74: 442-4.
- 5 Bourne WM. One year observation of transplanted human corneal endothelium. *Ophthalmology* 1982; 89: 600-4.
- 6 Forester RK, Fine M. Relation of donor age to success in penetrating keratoplasty. *Arch Ophthalmol* 1971; 85: 42-7.
- 7 Leibowitz HM. *Corneal disorders, clinical diagnosis and management*. 1st ed. Philadelphia: Saunders, 1984: 100-20.
- 8 Buxton JN. Keratoconus in symposium on contact lenses. *Trans New Orleans Acad Ophthalmol* 1973; 3: 88-100.
- 9 Woodward EG. Keratoconus: epidemiology. *J Br Contact Lens Assoc* 1984; 7: 64-76.
- 10 Copeman PWM. Eczema and keratoconus. *Br Med J* 1965; ii: 977-8.
- 11 Spincer WH, Fisher JJ. The association of keratoconus with atopic dermatitis. *Am J Ophthalmol* 1959; 47: 322-4.
- 12 Urrets-Zavalía A. Fixed, dilated pupil, iris atrophy and secondary glaucoma. *Am J Ophthalmol* 1963; 56: 257-65.
- 13 Davies PD, Ruben M. The parietic pupil: its incidence and aetiology after keratoplasty for keratoconus. *Br J Ophthalmol* 1975; 59: 223-8.
- 14 Chandler JW, Kaufmann HF. Graft reactions after keratoplasty for keratoconus. *Am J Ophthalmol* 1974; 77: 543-7.
- 15 Trautman RC, Lambers MA. Penetrating keratoplasty for keratoconus. *Cornea* 1987; 6: 289-305.
- 16 Abbot RL, Forester RK. Determinant of graft clarity in penetrating keratoplasty. *Arch Ophthalmol* 1979; 97: 1071-5.
- 17 Paglen PG, Fine M, Abbot RL, Webster RG. The prognosis for keratoplasty in keratoconus. *Ophthalmology* 1982; 89: 651-4.

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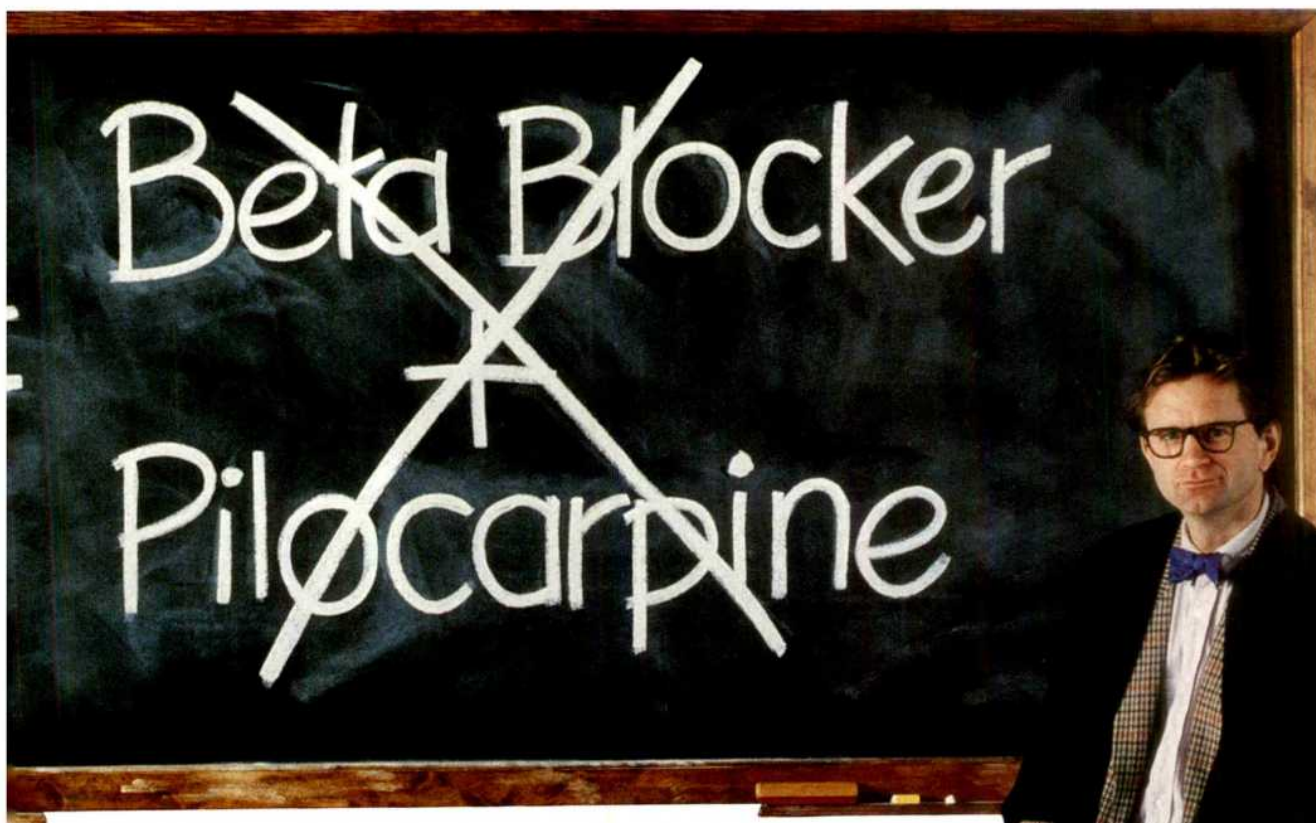


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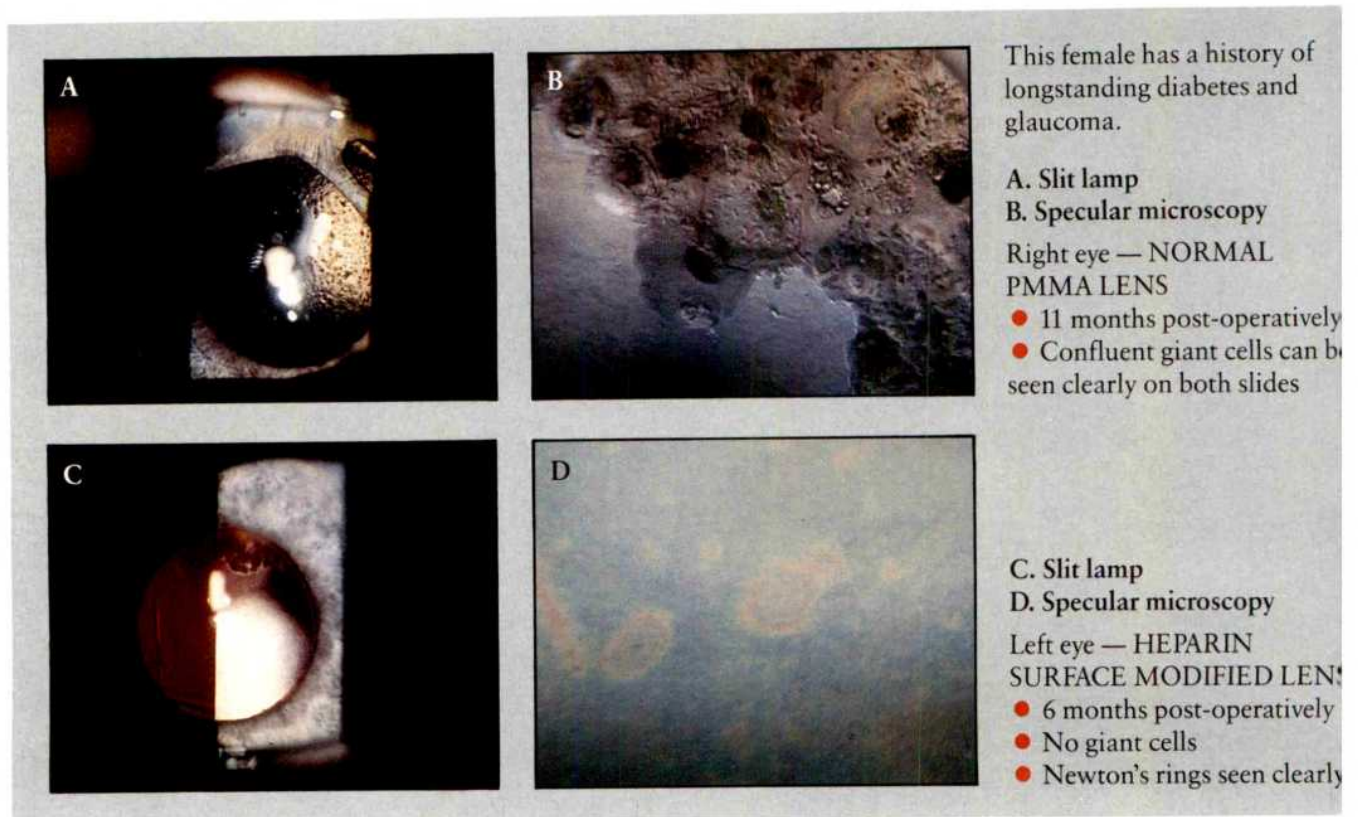
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Genetic counselling in retinoblastoma: importance of ocular fundus examination of first degree relatives and linkage analysis

Z Onadim, P G Hykin, J L Hungerford, J K Cowell

Abstract

We report an unusual family pedigree segregating the retinoblastoma predisposition gene. Expression of the phenotype in different individuals in this family ranges from asymptomatic gene carriers, regressed tumours, through unifocal to bilateral multifocal lesions. Because of the unusual pattern of inheritance in this family, initial genetic counselling at a local hospital did not take into account the possibility of incomplete penetrance of the gene, and complete ophthalmological examination of unaffected family members was not undertaken. We have used DNA probes from within the retinoblastoma predisposition gene for unequivocal identification of gene carriers. The subsequent demonstration of regressed tumours in founder members of the family confirmed the diagnosis of a dominantly inherited disease. The circumstances of the management of this family emphasises the need for specialist ophthalmic examination of first degree relatives and detailed genetic analysis of all such families with DNA probes.

Retinoblastoma (RB) is the commonest primary malignant intraocular tumour in children and has both hereditary and sporadic forms. In familial cases the inheritance follows an autosomal dominant pattern, usually with high penetrance. Thus offspring of gene carriers have a 50% risk of inheriting the mutant gene. Although the retinoblastoma phenotype shows a dominant mode of inheritance, it is clear that at the cellular level additional mutations are required, since not all retinal cells produce tumours, and in approximately 10% of gene carriers tumours do not develop at all. This latter phenomenon is referred to as incomplete penetrance. Knudson¹ showed in a statistical analysis of RB that a single additional mutation was sufficient for tumorigenesis. This second mutation occurs sporadically in the homologous normal RB gene in retinal precursor cells.² Hereditary cases are usually affected bilaterally, and, since the probability of the second mutation occurring is relatively high, the mean number of tumours in each eye averages four to five.

Retinoblastoma can also regress spontaneously,³ leaving characteristic retinal scars which often resemble successfully treated tumours. These may be compatible with normal visual acuity and remain undetected. The presence of multiple regressed tumours in a single individual or a single regressed tumour in an individual with relatives with RB implies gene carrier status for those individuals and puts their

children at approximately 50% risk of tumour development. It is essential therefore, to examine the retinae of parents of apparently sporadic cases.

The gene for RB predisposition – RB1 – was mapped to chromosome region 13q14 following observations that, in a small percentage of patients, predisposing constitutional chromosome deletions of this region were present.^{4,5} Genetic linkage analysis using the adjacent esterase-D gene confirmed that the hereditary non-deletion form of the disease was due to mutations on the same locus.⁶⁻⁸ The RB1 gene was isolated by several groups independently⁹⁻¹¹ and authenticated following the demonstration of mutations in this gene in tumour cells and predisposed persons.^{9,12-14} Individual unique DNA probes from within the genomic sequence of RB1, which recognised restriction fragment length polymorphisms (RFLPs), were isolated by Wiggs *et al*¹⁵ which now form the basis of linkage analysis in RB families.¹⁵⁻¹⁷ So far no cases have been reported of genetic recombination between these DNA probes and the disease phenotype, and they have been used successfully in prenatal and perinatal prediction of carrier status.^{17,18}

Despite the now well characterised genetics of retinoblastoma and the availability of genetic probes for screening and counselling, advice to some families is still sometimes incomplete. This is most often the case in families where the phenotype segregates with unusual characteristics. In this report we present the details of one such family as an example of the difficulty in making the correct prediction in the absence of genetic linkage data and ophthalmic examination of first degree relatives.

Materials and methods

DNA was prepared from white blood cells and lymphoblastoid cell lines by standard methods.¹⁹ All procedures for the analysis of DNA samples were as described previously.¹⁷

Results

The family pedigree is shown in Figure 1. The parents (II.6 and II.7) of the affected twins are first cousins and each has a sister affected by unilateral retinoblastoma. These observations are consistent with one or both of their parents (I.2 and I.3) being unaffected gene carriers. Family counselling was sought at a local hospital by the mother (II.7). In 1984, prior to their birth, a diagnosis of an autosomal recessive disorder was given at the local hospital by virtue

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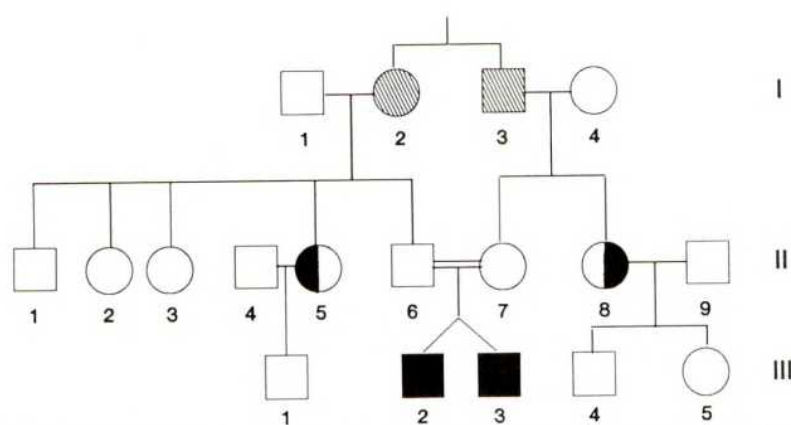


Figure 1 Family pedigree showing the segregation of the retinoblastoma phenotype. □=male. ○=female. ■=affected bilaterally. ●=affected unilaterally. ⊙=regressed tumours.

of the fact that both parents had an affected sib, and a risk of having affected children of 1:32 was given. The retinæ of the parents, I.2 and I.3, were not examined at this time.

In February 1987 non-identical twins were born, and in June of that year a diagnosis was made of bilateral retinoblastoma in both children at the age of 4 months following their referral to St Bartholomew's Hospital for treatment. Proband 1 had a juxtapapillary RB in the right eye and a posterior pole tumour in the left eye. Proband 2 had an RB nasal to the optic disc in the left eye and later developed a tumour temporal to the posterior pole in the right eye. No evidence of extraocular spread was discovered in either proband.

In July 1987 both grandparents attended the ophthalmology clinic at St Bartholomew's Hospital, where I.3 was found to have a large, grey translucent lesion at the posterior pole of the left eye (Fig 2). I.2 was found to have a small posterior pole lesion of the right eye which was translucent with pigment epithelial disturbance (Fig 3), and a small lesion nasal to the optic disc in the left eye. These lesions were typical of spontaneously regressed RB. Close examination of the retinæ of II.6 and II.7 showed no evidence of retinal scarring. Esterase-D studies showed all family members to be genotype 1-1. Chromosome analysis showed no deletions of the 13q14

locus in any family member. At the time of the initial consultation DNA-based analysis was not generally available.

Since both parents are potentially unaffected gene carriers, there is a possibility that their children could be homozygous for the RB gene mutation. To investigate this possibility we used the intragenic RB DNA probe RS2.0,¹⁵ which recognises an 8 allele variable number tandem repeat (VNTR). We were able to follow the segregation of the chromosome 13 in this family, the details of which are given in figures 4 and 5. Not all family members were available for analysis, and only the alleles for those from whom blood samples were obtained are shown.

Analysis of patients II.5 and II.8, the affected cousins, shows that the common alleles are 1·9, which must have been derived from gene carriers I.2 and I.3. Since both I.2 and I.3 showed evidence of retinal scarring it must be assumed that the 1·9 allele came from a common ancestor carrying the predisposing gene. Both parents II.6 and II.7 also carry the 1·9 allele. For II.6 this allele was inherited from I.2 but II.7 received the 1·5 allele from her father and the 1·9 allele from the unrelated parent I.4. We would predict therefore that II.7 is not a gene carrier, thus excluding the possibility that their children could become homozygous for this mutation. The twins have inherited the 1·9 allele from their father, confirming the cosegregation of the RB phenotype with this allele. Analysis of the other members of the family shows that II.1 is definitely not a gene carrier, since the 1·9 allele is missing, but, being homozygous for 1·9, II.2 must be an asymptomatic gene carrier.

The affected patient II.5 is now homozygous for the 1·9 allele, which means that this probe will not be useful for future prenatal screening. In contrast II.8 is heterozygous and could be offered prenatal screening in the future. The so far unaffected child in this family unit, III.4, is also homozygous for the 1·9Kb allele, which places him at high risk for tumour development.

Discussion

In this unusual pedigree segregating the retino-

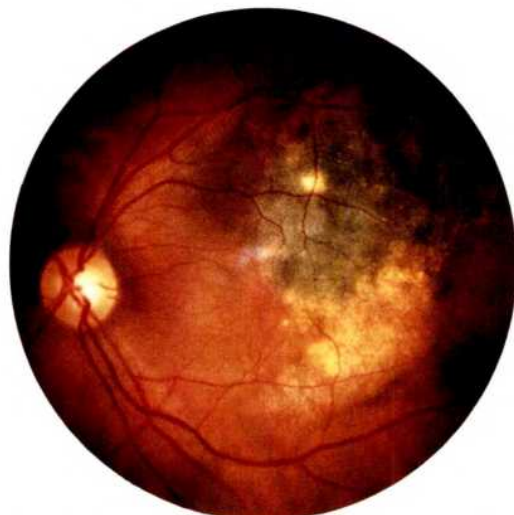


Figure 2 Large spontaneously regressed retinoblastoma at the posterior pole of the left eye of I.2.

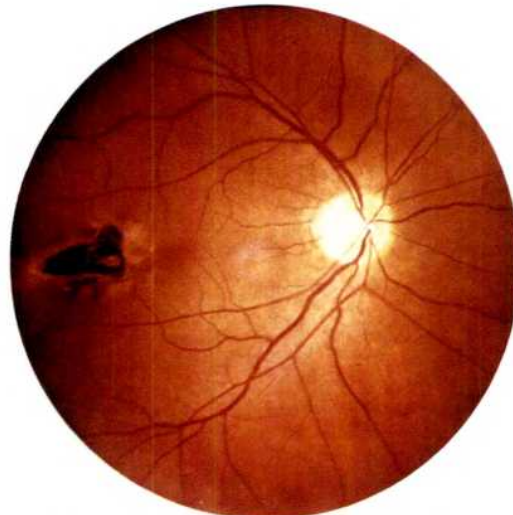


Figure 3 Small regressed retinoblastoma at the posterior pole of the right eye of I.3.

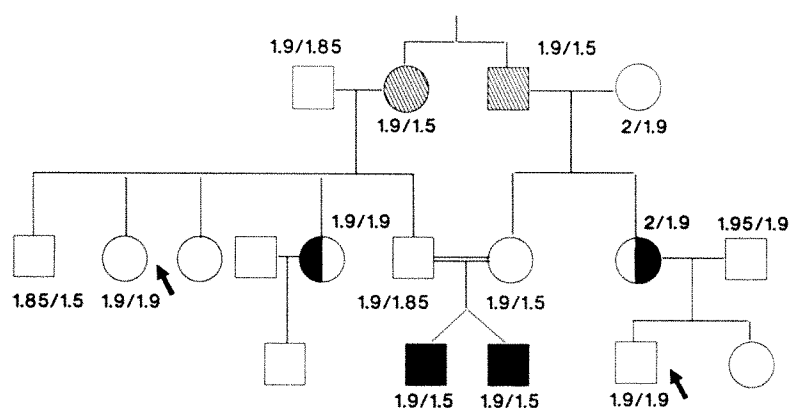


Figure 4 Segregation of the alleles identified by the RS2.0 DNA probe. The mutant retinoblastoma gene is segregating with the 1.9 allele. Asymptomatic gene carriers are indicated by the arrows. Symbols as in Figure 1.

counselling. The segregation of the RB phenotype with the 1.9 kb allele in the core family allowed us to identify an unaffected gene carrier who has not yet begun her own family. Although this individual is homozygous for the 1.9 kb allele, and so would not qualify for prenatal screening with this probe, new screening procedures are being introduced with other polymorphisms which could be used. For individual II.8, who is heterozygous for the RS2.0 polymorphism, prenatal screening is available. The same service can be offered to the twins. We have also demonstrated that the parents of the twins are not both gene carriers, which excludes the possibility of their having children homozygous for the mutation. Since such homozygous individuals have not been reported, it is not clear

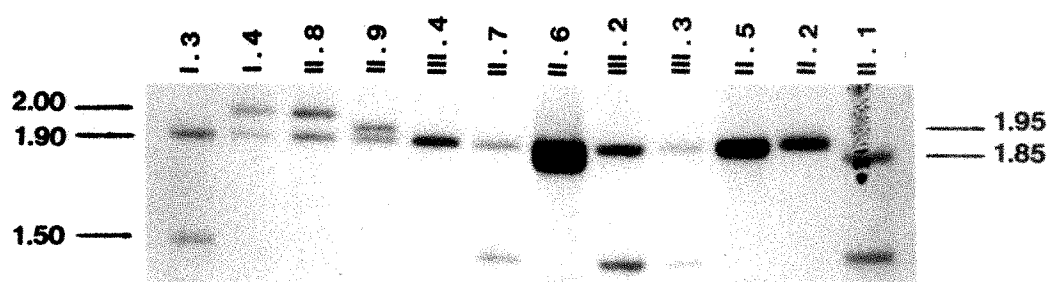


Figure 5 Southern blot analysis of key members of family RB-29 using the intragenic VNTR DNA probe RS2.0. In this family five different alleles 2.0 kb, 1.95 kb, 1.90 kb, 1.85 kb, and 1.5 kb are segregating. The RB predisposition gene segregates with the 1.9 kb allele.

blastoma predisposition gene there are both asymptomatic gene carriers and individuals with regressed tumours. In the second generation only unilaterally affected individuals are seen, which is unusual for predisposition gene carriers.¹ We have observed several similar families¹⁷ in the past where the mutation appears to predispose to a 'milder' form of the disease, and there are other examples in the literature.²⁰ At the time of the first counselling sessions, before the patients were referred to St Bartholomew's Hospital, linkage/deletion analysis using the esterase-D polymorphism was in general use in the UK,^{8,21} though, being of genotype 1-1, this family would not have been informative. Recombinant DNA probes were not generally available until 1987. Examinations of apparently unaffected relatives, however, would have altered the advice given, and in our view this is an important first step in counselling such families. Because of the unusually low penetrance of the gene mutation in some families, this should be extended as far back in the pedigree as possible. Since the ophthalmoscopic appearance of regressed tumours may fall outside the experience of some ophthalmological practices, families or individuals should be referred to specialist centres for examination.

The identification of spontaneously regressed tumours in the grandparents in this case raised the risk to the children to 1:2 compared with the 1:32 risk offered at the time of first consultation. By establishing the phenotypes for the majority of the members of this family it was possible to perform linkage analysis with DNA probes. This analysis established several important points for

what the expected phenotype might be, especially in 'mildly affected' pedigrees.

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- Knudson AG. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci USA* 1971; 68: 820-3.
- Cavenee WK, Hansen MF, Nordenskjold M, *et al*. Genetic origin of mutations predisposing to retinoblastoma. *Science* 1985; 228: 501-3.
- Gallie BL, Ellsworth RM, Abramson DH, Phillips RA. Retinoblastoma: spontaneous regression of retinoblastoma or benign manifestation of the mutation? *Br J Cancer* 1982; 45: 513-21.
- Lele KP, Penrose LS, Stallard HB. Chromosome deletion in a case of retinoblastoma. *Ann Hum Genet* 1963; 27: 171-4.
- Vogel W. The genetics of retinoblastoma. *Hum Genet* 1979; 52: 1-54.
- Sparkes RS, Murphree AL, Lingua RW, *et al*. Gene for hereditary retinoblastoma assigned to human chromosome 13 by linkage to esterase-D. *Science* 1983; 217: 971-3.
- Mukai S, Rapaport JM, Shields JA, Augsburger JJ, Dryja TP. Linkage of genes for human esterase-D and hereditary retinoblastoma. *Am J Ophthalmol* 1984; 97: 681-5.
- Cowell JK, Jay M, Rutland P, Hungerford J. An assessment of the usefulness of electrophoretic variants of esterase D in the antenatal diagnosis of retinoblastoma in the United Kingdom. *Br J Cancer* 1987; 55: 661-4.
- Friend SH, Bernards R, Rogelj S, *et al*. A human DNA segment with properties of the gene that predisposes to retinoblastoma and osteosarcoma. *Nature* 1986; 323: 643-6.
- Fung YT, Murphree AL, T'Ang A, Qian J, Hinrichs SH, Benedict WF. Structural evidence for the authenticity of the human retinoblastoma gene. *Science* 1987; 236: 1657-61.
- Lee WH, Bookstein R, Hong F, Young L, Shew JY, Lee EP. Human retinoblastoma susceptibility gene: cloning, identification and sequence. *Science* 1987; 235: 1394-9.
- Dunn JM, Phillips RA, Becker A, Gallie BL. Identification of germline and somatic mutations affecting the retinoblastoma gene. *Science* 1988; 241: 1797-800.
- Mitchell CD, Cowell JK. Predisposition to retinoblastoma due to a translocation within the 4-7R locus. *Oncogene* 1989; 4: 253-7.
- Higgins MJ, Hansen MF, Cavenee WK, Lalande M. Molecular

- detection of chromosomal translocations that disrupt the putative retinoblastoma susceptibility locus. *Mol Cell Biol* 1989; **9**: 1-5.
- 15 Wiggs J, Nordenskjeld M, Yandell D, *et al*. Prediction of the risk of hereditary retinoblastoma using DNA polymorphisms within the retinoblastoma gene. *N Engl J Med* 1988; **318**: 151-7.
- 16 Scheffer H, Te Meerman GJ, Kruize YCM, *et al*. Linkage analysis of families with hereditary retinoblastoma: non-penetrance of mutation, revealed by combined use of markers within and flanking the RB1 gene. *Am J Hum Genet* 1989; **45**: 252-60.
- 17 Onadim Z, Mitchell CD, Rutland PC, *et al*. Application of intragenic DNA probes in prenatal screening for retinoblastoma gene carriers in the United Kingdom. *Arch Dis Child* 1990; **65**: 651-6.
- 18 Mitchell CD, Nicolaides K, Kingston J, Hungerford J, Jay M, Cowell JK. Prenatal exclusion of hereditary retinoblastoma. *Lancet* 1988; **i**: 826.
- 19 Maniatis T, Fritsch EF, Sambrook J, eds. *Molecular cloning: a laboratory manual*. New York: Cold Spring Harbour Press, 1982: 1-406.
- 20 Connolly MJ, Payne RH, Johnson G, *et al*. Familial, EsD-linked, retinoblastoma with reduced penetrance and variable expressivity. *Hum Genet* 1983; **65**: 122-4.
- 21 Cowell JK, Rutland P, Jay M, Hungerford J. Deletions of the esterase-D locus from a survey of 200 retinoblastoma patients. *Hum Genet* 1986; **72**: 164-7.

Use of a central 10° field and size V stimulus to evaluate and monitor small central islands of vision in end stage glaucoma

Alan H Zalta

Abstract

In a retrospective review of 24 clinically stable eyes with small central islands of vision due to end stage glaucoma the combined use of a central 10° program and size V stimulus (10-2 with V) measured visual function undetected on a central 30° field tested with both the standard size III and non-standard size V stimuli. Furthermore, the mean sensitivity of the 10-2 with V remained stable on serial field testing (mean 3.9 examinations) on long term follow-up (mean 22.2 months). This study suggests that in end stage glaucoma the size V target is the stimulus of choice and a central 10° field may be the program of choice of evaluating and monitoring small central islands of vision.

Most routine automated threshold perimetry is performed with a central 30° program and size III stimulus (4 mm²). With these standard test parameters, central fields may be non-measurable or have minimal thresholds in conditions with severe field loss. Under these circumstances the usefulness of field testing for long term monitoring is severely limited. Using the larger No. 5 stimulus (64 mm²), Wilensky and co-workers¹ measured visual function in areas considered absolute scotomas with the standard sized stimulus. Use of the larger sized stimulus may yield enough additional information to warrant future field monitoring with the No. 5 stimulus for all subsequent examinations.¹

In end stage glaucoma a small island of tunnel vision and a temporal island are all that remain of the central field. When the central island is evaluated with a standard 30° field, the 16 test loci within 13° of fixation are the major locations of measured visual function. In the absence of measurable field between 15° and 30° it would seem more practical to monitor a small central island of vision with a central 10° program. To my knowledge there have been no investigations of a central 10° program in end stage glaucoma. This study examines retrospectively the usefulness of combining a central 10° program and size V stimulus (10-2 with V) in evaluating and monitoring small central islands of vision in end stage glaucoma.

Materials and methods

Central static threshold visual fields of all patients in my glaucoma referral practice with end stage glaucoma damage were reviewed retrospectively to identify those in which the 10-2 with V program was performed and followed up

for at least one year. An eye classified as end stage glaucoma had a cup-to-disc ratio greater than or equal to 0.9 and a central island of vision less than 13° on a central 30° field tested with the standard size III stimulus (30-2 with III).

To avoid potentially confounding variables I excluded eyes with a visual acuity less than 20/40, clinically unstable intraocular pressure, and consistently unreliable visual fields. Clinically unstable intraocular pressures were defined by any single intraocular pressure greater than 21 mmHg or a mean intraocular pressure greater than 17 mmHg during the follow-up period. These intraocular pressure criteria were selected to be strict enough to ensure that the glaucoma was adequately controlled with a high degree of probability, yet flexible enough to allow for an isolated increase of intraocular pressure into a borderline range which was subsequently controlled with additional treatment. Unreliable visual fields were defined by fixation losses or false positive errors greater than 25%. False negative errors were not used in defining reliability because of the low number of catch trials in the presence of severe visual field loss.

All central static threshold visual fields were performed on the Humphrey Field Analyser Model 620, an automated, computer-driven projection perimeter. All eyes were tested with the 10-2 with V program as well as the standard 30-2 with III and non-standard 30-2 with V programs.²⁻⁴ The central 10-2 program tests 68 points, equally spaced 2° apart and offset from the horizontal and vertical meridians by 1°. The central 30-2 program tests 76 points, equally spaced 6° apart and offset from the horizontal and vertical meridians by 3°. All first visual fields were performed with a 'full' threshold strategy and all subsequent examinations with a 'full from prior' threshold strategy, the patient's most recent test results being used as a starting point for re-examination. All eyes had serial field testing with 10-2 with V program alone or in combination with either the 30-2 with III or 30-2 with V programs. While the field analyser was updated with software revisions as they became available, all visual fields were analysed by Statpac Plus. The software compares the patient's measured threshold values with an age related normal database in programs using the standard size III stimulus, a feature incorporated into Statpac, and to mathematically derived 'normal' values based on a slope equation in programs using the non-standard size V stimulus.

The 'first' fields of all eyes performed with each program were examined for the mean deviation (30-2 with III) or mean sensitivity

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(30-2 with V and 10-2 with V), the percentage of loci with measurable thresholds within 13° of fixation, and the number of quadrants with no detectable threshold – that is, 0 dB, at 4.2° from fixation per quadrant. The parameters of 13° and 4.2° were selected so as to include the loci at the four diagonal positions 9° ($9^\circ \times 1.414 = 12.7^\circ$ eccentricity) and 3° ($3^\circ \times 1.414 = 4.2^\circ$ eccentricity) from the horizontal and vertical meridians. A subgroup of 50% of eyes with the lowest mean deviations on the 30-2 with III program were also compared with respect to their mean sensitivities on 30-2 with V and 10-2 with V programs. The value mean deviation used with the size III stimulus reflects the average deviation of sensitivity from a normal population of the same age, while the value mean sensitivity used with the size V stimulus does not take age or a normal population into account.

Moreover, the first 30-2 with V examination for each eye was evaluated for the presence of test loci with measurable thresholds in Bjerrum's region between 15° and 25°. For serial visual field examinations the number of fields performed and length of follow-up with each program were determined. The mean deviation of the 30-2 with III program and the mean sensitivity of the 30-2 with V and 10-2 with V programs were the indices used to determine stability or change on serial examination.

The means were compared by a correlated-samples *t* test. Frequencies were compared by McNemar's test. A repeated-measures analysis of variance was performed on the mean sensitivity of serial 10-2 with V fields, the mean deviation of serial 30-2 with III fields, and the mean sensitivity of serial 30-2 with V fields. The actual calculations were made with the App-Stat software package for the Apple IIe computer.⁵ The standard two-tailed 0.05 significance level was used.

Results

Twenty-four eyes in 18 patients fulfilled the study criteria. The mean length of follow-up for visual fields performed with the 10-2 with V program was 22.2 months (SD 4.9 months). The mean intraocular pressure of all eyes during the follow-up period was 15.0 mmHg (SD 1.4 mmHg). The mean age of the patients was 73.5 years (SD 9.5 years).

Table 1 shows the 'first' field data for the mean deviation of the 30-2 with III program and the mean sensitivity of the 30-2 with V and 10-2 with V programs. The mean sensitivity for the 10-2 with V program was significantly greater than for the 30-2 with V program for all 24 eyes ($p < 0.001$) and for 50% of eyes with the lowest mean deviation on 30-2 with III ($p < 0.001$). Coincidentally, this subgroup also had the 12 lowest mean sensitivities on the 30-2 with V. Fig 1 is an example of the numeric threshold and grey-tone printouts from the three field programs of an eye in this subgroup.

Table 2 shows the percentage of measurable loci within 13° and the number of eyes with absolute loss at 4.2° from fixation per quadrant on the first fields of all three programs. The percentage of loci with measurable thresholds

Table 1 Mean deviation (30-2 with III) and mean sensitivity (30-2 with V and 10-2 with V) of first fields (in dB)

	All eyes (n=24)		50% of eyes (n=12)*	
	Mean	SD	Mean	SD
30-2 with III	-25.79	3.15	-28.27	1.39
30-2 with V	6.60	6.32	1.50	1.95
10-2 with V	15.58†	7.27	12.33†	8.28

*Eyes with lowest mean deviations on 30-2 with III.

† $p < 0.001$ compared with 30-2 with V.

within 13° was significantly greater for the 10-2 with V compared with both the 30-2 with V ($p < 0.001$) and 30-2 with III ($p < 0.001$) and for the 30-2 with V compared to the 30-2 with III ($p < 0.001$). The number of eyes with detectable thresholds at 4.2° from fixation was significantly greater with both the 30-2 with V program ($p = 0.003$) and 10-2 with V program ($p < 0.001$) as compared with the 30-2 with III program. However, there was no significant difference between the 30-2 with V and 10-2 with V programs. Further, on the central 30° program 10 of 24 eyes had measurable thresholds in Bjerrum's region from 15° to 25° by the size V stimulus in at least one quadrant. These same areas were considered absolute scotomas with the standard sized III stimulus.

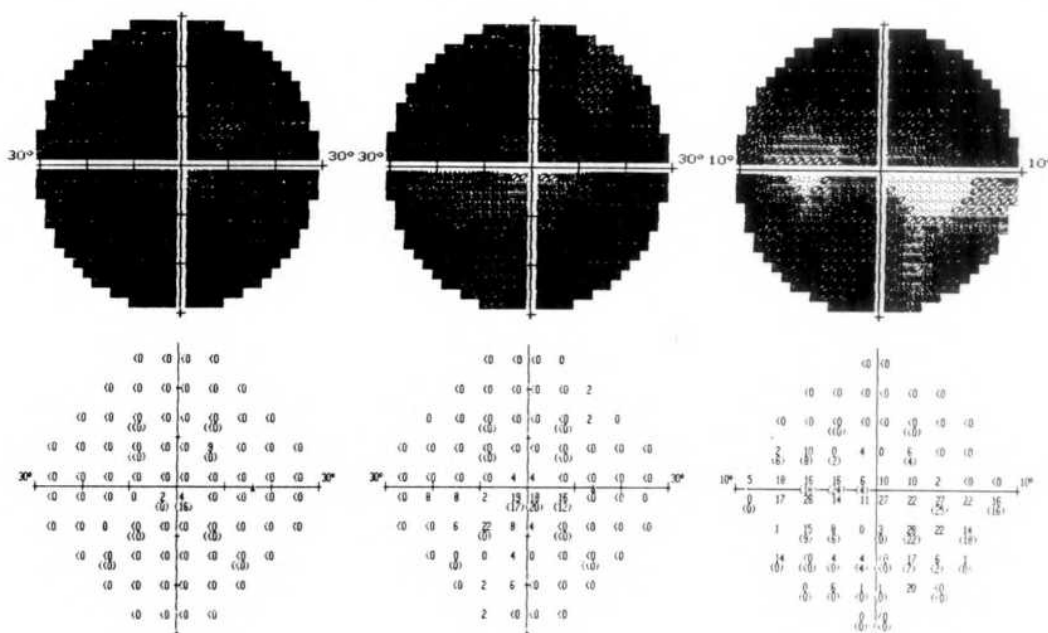
Table 3 shows the number of eyes tested, number of serial visual fields, and length of follow-up for each field program. Of the 24 eyes followed up serially with the 10-2 with V, eight were simultaneously followed up with the 30-2 with III, and 11 other, different, eyes were simultaneously followed up with the 30-2 with V. There was no significant difference on serial field testing of the mean sensitivity of the 10-2 with V and 30-2 with V programs and the mean deviation of the 30-2 with III program during their respective follow-up periods. Fig 2 shows the grey-tone printouts of six serial fields using the 10-2 with V program on the eye in Fig 1.

Discussion

In end stage glaucoma the central visual field is a tiny island of vision in a sea of darkness. With automated threshold perimetry these central fields may be unmeasurable or have minimal thresholds by the standard test parameters, namely, a 30° field and size III stimulus. To my knowledge this study is the first investigation examining the combined use of a central 10° program and size V stimulus to evaluate and monitor small central islands of vision in end stage glaucoma. In a retrospective review of 24 clinically stable eyes with end stage glaucoma the 10-2 with V program measured visual function undetected with the 30-2 with III program. Furthermore, the mean sensitivity of the 10-2 with V program remained statistically unchanged on serial testing over a mean of 22 months. These findings suggest that the 10-2 with V program provides additional field information to evaluate the integrity of small central islands of vision and possibly to monitor their stability in the long term.

However, the 10-2 with V program may not

Figure 1 The numeric threshold and grey-tone printouts from the first 30-2 with III (left), 30-2 with V (middle), and 10-2 with V (right) of an eye with a small central island of vision due to end stage glaucoma.



be the optimal parameters for all eyes with end stage glaucoma. As with the 10-2 with V program, the 30-2 with V program measured visual function within 13° and at 4.2° from fixation undetected with the 30-2 with III program. In addition, in 42% of eyes the 30-2 with V program measured visual function between 15° and 25° in at least one quadrant.

These data support the findings of Wilensky and co-workers,¹ who first demonstrated that the size V stimulus measured visual function in areas considered absolute scotomas with the standard size III stimulus. However, the mean sensitivity of the 10-2 with V was 235% greater than the 30-2 with V for all eyes and 822% greater for the 50% of eyes with the least measurable fields. Within the central 13° the 2° spacing of test loci on the 10-2 with V program appears to provide additional field information not seen with 6° spacing on the

30-2 with V program. These findings suggest that in end stage glaucoma the size V target is the stimulus of choice and the 10° field may be more appropriate than the 30° field for evaluating and monitoring small central islands of vision which have minimal or non-existent thresholds in Bjerrum's region.

The psychophysical effects of varying target size in the visual field have been previously examined.⁶⁻⁸ It has been well established that spatial summation is larger in the peripheral retina, at low luminance levels, and for large stimuli.⁶ Owing to spatial summation a large stimulus is more easily seen than a smaller stimulus of the same luminance.⁶ Most automated perimeters use a standard 4 mm² stimulus size, equivalent to the Goldmann size III, because it creates the greatest dynamic range of differential light sensitivity in the visual field.^{6,9} The smaller size I stimulus at maximum intensity is not strong enough to quantify the depth of defects, and the size V stimulus is larger than some of the scotomas one may wish to detect.¹⁰ In end stage glaucoma with small central islands of visual field, spatial summation due to the larger size V stimulus allows measurement of significant visual function undetected by the standard size III stimulus. In this population use of the size V stimulus appears to have practical advantages over the standard size III stimulus in measuring and following serial fields over time.

The 50% of eyes with the least measurable fields had non-existent or virtually non-existent thresholds when the 30-2 with III and 30-2 with V programs were used. The severity of field loss in this subgroup, as seen in the example of Fig 1, precludes a meaningful prospective evaluation with standard testing parameters. Eyes with less severe field loss would have to be used in a prospective comparison of the 10-2 with V and 30-2 with III programs. Furthermore, a prospective study should control the frequency and number of visual fields. This would eliminate the possibility of self selection by patients and provide a more meaningful comparison of the serial fields. A prospective

Table 2 Measurable loci within 13° and absence of detectable thresholds at 4.2° from fixation on the first field of the 30-2 with III, 30-2 with V, and 10-2 with V programs (n=24 eyes)

Visual field program	Percentage of loci with thresholds >0 dB within 13°		Number of eyes with no detectable threshold at 4.2° from fixation per quadrant			
	Mean	SD	1 quad	2 quads	3 quads	4 quads
30-2, III	37.8	21.2	18	15	9	3
30-2, V	58.9†	25.4	7†	3	2	1
10-2, V	87.5‡§	25.0	5‡	2	1	0

*The 30-2 with III and 30-2 with V have 16 test loci and the 10-2 with V program has 68 test loci within 13 degrees from fixation.

†p<0.01 compared to 30-2 with III.

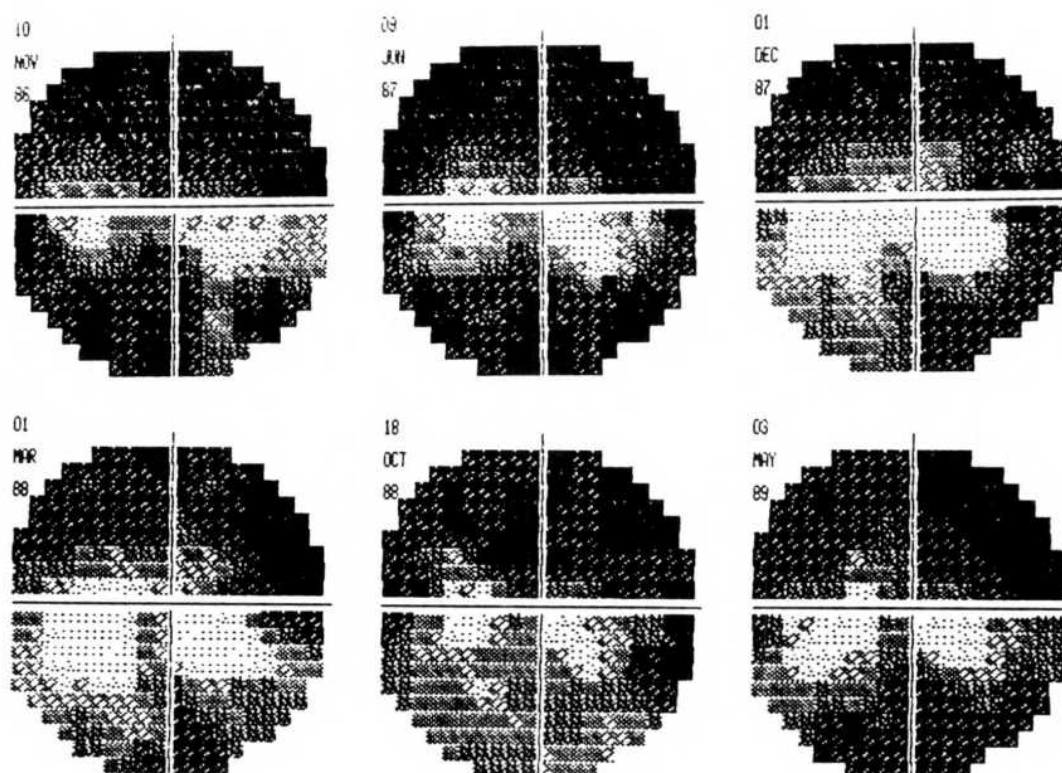
‡p<0.001 compared to 30-2 with III.

§p<0.001 compared to 30-2 with V.

Table 3 Number of eyes tested, number of serial visual fields, and length of follow-up with each program

Visual field program	Number of eyes	Number of serial visual fields		Length of follow-up (in months)	
		Mean	SD	Mean	SD
10-2 with V	24	3.9	1.6	22.2	4.9
30-2 with V	11	4.8	1.3	20.6	8.9
30-2 with III	8	5.8	2.3	26.0	8.1

Figure 2 The grey-tone printouts of six serial fields performed over 2½ years using the 10-2 with V program on the eye in Fig 1. On linear regression analysis, the mean sensitivity slope, $+1.1$ (SD 3.8) dB/year, was not significant, $p \geq 5\%$.



study should also consider monitoring the temporal peripheral island of vision, which is often quite large and prominent in end stage glaucoma. Evaluation of these temporal islands of vision would require peripheral field testing with the 30/60-2 program, an effort which was not undertaken in the current study.

For central threshold perimetry in end stage glaucoma retaining a small central island of vision I recommend that eyes with a mean deviation greater than -20 dB using a 30° field with size III stimulus should have additional 30° field testing using a size V stimulus. Furthermore, eyes with a mean deviation greater than -25 dB using a 30° field with the size III stimulus should have additional field testing using a 10° program with the size V stimulus. As the use of non-standard parameters in automated threshold perimetry becomes more commonplace, a normal reference population database will become necessary to facilitate the development of statistical parameters other than mean sensitivity. This effort would further enhance our

ability to evaluate and monitor severe visual field loss.

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- 1 Wilensky JT, Mermelstein JR, Siegel HG. The use of different-sized stimuli in automated perimetry. *Am J Ophthalmol* 1986; **101**: 710-3.
- 2 Humphrey field analyzer operator's manual: model 620. San Leandro: Allergan Humphrey, 1983.
- 3 Heijl A, Lindgren G, Olsson J. A package for the statistical analysis of visual fields. *Doc Ophthalmol Proc Ser* 1987; **49**: 153-68.
- 4 New software releases for the Humphrey field analyzer and Statpac Plus. San Leandro: Allergan Humphrey, 1988.
- 5 APP-STAT Statistical Package for Apple II Computers. Tulsa: Statsoft, 1986.
- 6 Fankhauser F. Problems related to the design of automated perimeters. *Doc Ophthalmol* 1979; **47**: 89-138.
- 7 Johnson CA, Keltner JL, Balestrery F. Effects of target size and eccentricity on visual detection and resolution. *Vision Res* 1978; **18**: 1217-22.
- 8 Sloan LL. Area and luminance of test object as variables in examination of the visual field by projection perimetry. *Vision Res* 1961; **1**: 121-38.
- 9 Fankhauser F. The development of computerized perimetry. In: Whalen WR, Spaeth GL, eds. *Computerized visual fields. What they are and how to use them*. Thorofare: Slack, 1985: 14.
- 10 Anderson DR. *Perimetry with and without automation*. 2nd ed. St Louis: Mosby, 1987: 43.

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Use of a blue filter in visual field analysis

Charles E Hugkulstone, Stephen A Vernon

Abstract

One hundred and twenty seven eyes of 127 patients were studied by means of a Kodak 47B Wratten blue gelatin filter in conjunction with the Friedmann Mark 1 visual field analyser. There were 49 patients in the normal group, 50 patients in the ocular hypertension group, and 28 patients in a group with early glaucoma. A simple scoring system did not show a useful difference between these three groups. However, use of a derived threshold value for each target group designated by the letters B to P (giving selective blue field scores) differentiated between normal subjects and those with early glaucomatous field loss. When used with a calculated upper limit of normal to give a specificity of 96%, this test had a sensitivity of 64%. Of the ocular hypertension group 22% gave abnormal results in comparison with normal persons. This simple adaptation to the Friedmann protocol may aid the ophthalmologist in the detection and confirmation of early glaucoma.

The diagnosis of chronic glaucoma generally rests on the triad of raised intraocular pressure, cupping of the optic disc, and a classical field defect. The diagnosis is straightforward when all three are present, but is less so in the early stages before unequivocal field defects develop.

Recent work has attempted to improve the sensitivity of detecting glaucomatous damage at an early stage. Blue light information is processed by larger sized ganglion cells (with corresponding differences in their axons) than red or green light,¹ and it has been found that the larger diameter axons are selectively damaged by glaucoma.² Blue colour vision defects have been shown to occur in glaucoma and ocular hypertension³ and also to be related to the highest recorded intraocular pressure in patients with glaucoma.⁴ However, these tests require sophisticated and expensive equipment.

Only one study has investigated the use of a blue stimulus with a standard central field analyser,⁵ but it found no advantage for it over a white stimulus, though normal subjects were not studied. This paper presents the findings of a study by a different technique using a blue filter with a Friedmann central visual field analyser in normal subjects, ocular hypertensives, and patients with early chronic simple glaucoma.

Patients and methods

Subjects were selected from patients attending two separate ophthalmic outpatient departments who had a visual acuity of at least 6/18 unaided and 6/9 or better aided. Classification into the three groups (normal, ocular hypertension, or glaucoma) was based on the worse eye (that is, by

patient). If both eyes were eligible for this study, then only one was randomly included in the statistical analysis.

Normal subjects were required to have an intraocular pressure of 21 mmHg or less and healthy fundi with normal optic discs. Patients with glaucoma were defined by an intraocular pressure >21 mmHg without treatment, pathological cupping of the optic disc, and at least three adjacent spots of reduced sensitivity on field testing with the Friedmann Mark 1 analyser. However, if an eye had more than four points of absolute field loss per vertical hemifield, that eye was excluded from analysis, because we were concentrating on cases of early glaucoma only. The ocular hypertension group included patients with a similarly raised intraocular pressure but without visual field loss to a white target or specific pathological features on disc examination. Patients using miotic eye drops were excluded, as were known diabetics.

All patients gave verbal consent after the nature and purpose of this investigation had been explained to them.

The test was performed with the Friedmann Mark 1 visual field analyser without any spectacle correction. The threshold value for a white stimulus was determined by means of the four points 2.5° from fixation (target group P). The neutral density filter was started at 2.4 log units, and subjects were allowed three attempts at this value. This was then reduced by steps of 0.2 log unit until at least two of the four targets were seen in two out of the three attempts. This value was defined as the threshold, which was then reduced by a further 0.4 log unit to run the test (the working value). The four extreme peripheral points (target group A) were ignored, and subjects were allowed three attempts at the working value for the remaining targets. If any points were missed, the filter setting was reduced by 0.2 log unit and a further three attempts were allowed at the new setting. This process was repeated until all the points were seen, and the highest filter setting for each point was recorded on a standard chart.

Once the test was completed for the white stimulus, a Kodak 47B Wratten blue gelatin filter mounted in a spectacle frame (with an occluder set in front of the fellow eye) was worn by the subject. We then repeated the test using the same protocol as above, but, unlike the previous report of this technique,⁵ we used the working value already determined for the white stimulus. A separate standard chart was used to record the highest filter setting found for each point with the blue stimulus.

Initially a simple scoring system was applied to the blue field. This gave 1 point for each 0.2 log unit decrease from the working value found for all targets.

A further scoring system was also employed,

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Table 1 Mean (SD) values for blue field and selective blue field (SBF) scores

	Blue field score	SBF score
Normal	22.3 (25.6)	7.5 (6.2)
Ocular hypertension	31.8 (30.7)	12.7 (10.4)
Glaucoma	55.2 (31.8)	28.7 (15.8)

termed the selective blue field (SBF). The SBF was obtained by considering the filter settings used for each one of the 14 groups of two to four individual targets when recording the blue field. The highest value recorded for any one of these points was treated as the threshold value for that particular target group. The remaining points in the group were then given a score of 1 point for each 0.2 log unit reduction from this derived 'setting threshold'. These were then recorded on to a third standard chart, and their total score noted.

Statistical analysis was performed with the unpaired *t* test. Values are given as mean (standard deviation) unless otherwise noted.

Results

In total 127 patients were studied. These were divided into 49 patients in the normal group, 50 in the ocular hypertension group, and 28 in the early glaucoma group. A further two patients were unable to see the fixation target when wearing the blue filter and were excluded from the study. The mean ages of these three groups, 58.7 (10.2), 62.0 (11.7), and 63.4 (9.8) years respectively, showed no significant difference.

The mean blue field scores are shown in Table 1. Although there was a significant difference between the normal and glaucoma subjects, there was considerable overlap between all three groups because of the frequent generalised depression in sensitivity produced by the blue filter, especially within the central 10°. This is demonstrated by calculating an upper limit of normal as the mean + (1.96 × SD) from the results of the normal group. This gives a value of 72.5, which is greater than the mean scores for both the ocular hypertension (31.8) and the glaucoma groups (55.2). The blue field scores were therefore unhelpful in distinguishing patients with early glaucoma from normal subjects.

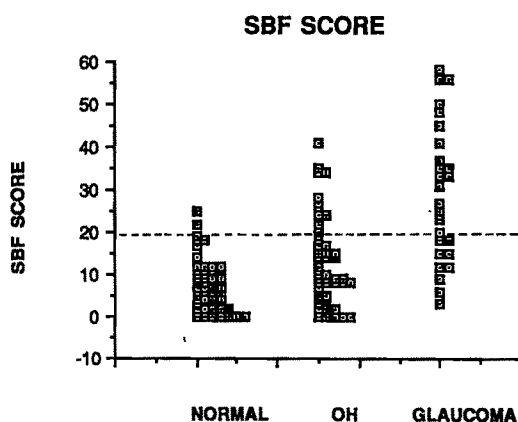


Figure 1 Scattergram of the selective blue field (SBF) scores for the three groups. Each point represents one eye of one patient. The dotted line represents the calculated upper limit of normal (see text). OH=ocular hypertension.

The SBF scoring system was developed to try to remove this background noise. Table 1 also shows the mean SBF scores for all three groups. The score for normal subjects was significantly lower than for both the ocular hypertension group ($p < 0.01$) and the glaucoma patients ($p < 0.001$), while the ocular hypertensive patients also had a lower SBF score than those with glaucoma ($p < 0.001$). The distribution of SBF scores in the three groups is presented in Figure 1.

An upper limit of normal of 19.7 for the SBF score was calculated in the same way as for the blue field score mentioned above. When this was applied to the ocular hypertensive group, although the mean score (12.7) was below the upper limit of normal, 11 subjects (22%) had values above it. In the early glaucoma group 18 patients (64%) had scores higher than the upper limit of normal, as was the mean score for this group (28.7).

The 10 eyes from the early glaucoma group that fall below the upper limit of normal were looked at more closely. Two had no field loss on standard testing with a white stimulus, but came from the patients whose diagnostic eye showed marked field loss and so was excluded from the analysis.

Discussion

The selection of subjects with good visual acuity was determined by the use of a spectacle frame to mount the blue filter. To prevent any artefacts arising from superimposing the blue filter frame over the patient's own spectacles we decided to test all subjects without any correction. By our choice of a minimum unaided acuity of 6/18, we excluded any large uncorrected refractive error which might have influenced the results. Low power spherical refractive errors have been shown to reduce threshold values, but this occurs with a similar magnitude at all eccentricities within the central 25°, and so should not affect our findings. However, it does mean that our results are confined to a select population, and further work would be required on patients whose visual acuities fall outside this range.

Although of interest, our original analyses using the blue field scores were clearly unhelpful in quantitatively distinguishing the glaucoma and normal groups. As mentioned above, this was because of the generalised depression in sensitivity with the blue field, particularly centrally, which the SBF was developed to counteract. We have demonstrated that the SBF score produces a marked difference between the normal and early glaucoma groups, with considerably less overlap.

In addition, when the specificity of the upper limit of normal for both SBF and blue field scores is set high at 96%, the SBF score sensitivity for patients with early glaucoma is 64%, in contrast to 25% for the blue field score. These values may reflect the relatively small numbers in the glaucoma group (all of whom had only early field changes), as the 95% confidence interval shows that the SBF sensitivity may range from 46% up to 82%. If the specificity is lowered to 90%, then the SBF sensitivity shows a

corresponding increase to 75% (95% confidence interval 59% to 91%). This requires only a small reduction in the value of the upper limit of normal to 17.5.

If the two eyes without field loss are excluded from the early glaucoma group, then the sensitivity for detecting early field loss rises to 69% (95% confidence interval 51% to 87%) for the original specificity of 96%. Lowering the specificity to 90% produces a sensitivity for early field loss of 81% (95% confidence interval 66% to 96%).

Of particular interest was the distribution of eyes in the ocular hypertensive group, with 22% having an abnormal SBF score. The main drawback with this observation is whether these scores are repeatable, and this does require further study. However, abnormalities of visual function in ocular hypertensive patients have been reported in other studies assessing colour vision,^{7,8} contrast sensitivity,⁹ and with pattern electroretinography.¹⁰

Epidemiological studies suggest that approximately 10% of patients with ocular hypertension develop the typical field defects of glaucoma when followed up for 10 years.^{11,12} Our ocular hypertensive group, because of referral practices, may contain a greater proportion who will convert to glaucoma. This analysis may therefore offer additional information for use when attempting to assess which of these patients may progress to develop field loss, though a prospective follow-up study is required to evaluate this.

Recently it has been found that the use of a blue stimulus on a yellow background allows the isolation of short wavelength sensitive cones, and can detect glaucoma-like field defects that are undetectable with a standard white stimulus.⁸ Since our subjects wore the blue filter, this effectively produces a blue background, which should not stimulate the long and medium wavelength sensitive cones, thus creating similar conditions to those employed by Heron and colleagues,⁸ but by a different and simpler technique. More recent work, again using a blue stimulus on a yellow background, has confirmed its ability to detect early glaucomatous damage.¹³ However, the authors also found that with dense defects (greater than 1.0 log unit) blue/yellow perimetry showed no advantage over standard perimetry.

Isolated missed points on a suprathreshold

screening programme are not uncommon in clinical practice,¹⁴ and they may cause considerable confusion. In the presence of an equivocal field defect on a white field an SBF score of 19 or less would indicate an 82% probability of normality. A score greater than this indicates a 90% probability of abnormality and would demand closer observation. However, this applies only to a typical hospital population of glaucoma suspects, where one-third of suspects would have early glaucoma.

In conclusion, although Logan and Anderson dismissed the use of a blue filter,⁵ we consider that its use, with our protocol, may aid the detection and confirmation of early loss of visual function in glaucoma suspects and merits further investigation.

We thank Mr T Arulampalam and Mr A S Rubasingham for kindly allowing us to study patients under their care.

- 1 de Monasterio FM. Asymmetry of on- and off-pathways of blue-sensitive cones of the retina of macaques. *Brain Res* 1979; **166**: 39-48.
- 2 Quigley HA, Sanchez RM, Dunkelberger GR, L'Hernault NL, Baginski TA. Chronic glaucoma selectively damages large optic nerve fibers. *Invest Ophthalmol Vis Sci* 1987; **28**: 913-20.
- 3 Gündüz K, Arden GB, Perry S, Weinstein GW, Hitchings RA. Color vision defects in ocular hypertension and glaucoma. Quantification with a computer-driven color television system. *Arch Ophthalmol* 1988; **106**: 929-35.
- 4 Yamazaki Y, Drance SM, Lakowski R, Schulzer M. Correlation between color vision and highest intraocular pressure in glaucoma patients. *Am J Ophthalmol* 1988; **106**: 397-9.
- 5 Logan N, Anderson DR. Detecting early glaucomatous visual field changes with a blue stimulus. *Am J Ophthalmol* 1983; **95**: 432-4.
- 6 Heuer DK, Anderson DR, Feuer WJ, Gressel MG. The influence of refraction on automated perimetric threshold measurements. *Ophthalmology* 1987; **94**: 1550-3.
- 7 Hamill TR, Post RB, Johnson CA, Keltner JL. Correlation of color vision deficits and observable changes in the optic disc in a population of ocular hypertensives. *Arch Ophthalmol* 1984; **102**: 1637-9.
- 8 Heron G, Adams AJ, Husted R. Central visual fields for short wavelength sensitive pathways in glaucoma and ocular hypertension. *Invest Ophthalmol Vis Sci* 1988; **29**: 64-72.
- 9 Ross JE, Bron AJ, Reeves BC, Emmerson PG. Detection of optic nerve damage in ocular hypertension. *Br J Ophthalmol* 1985; **69**: 897-903.
- 10 Weinstein GW, Arden GB, Hitchings RA, Ryan S, Calthorpe CM, Odom JV. The pattern electroretinogram (PERG) in ocular hypertension and glaucoma. *Arch Ophthalmol* 1988; **106**: 923-8.
- 11 David R, Livingston DG, Luntz MH. Ocular hypertension - a long-term follow-up of treated and untreated patients. *Br J Ophthalmol* 1977; **61**: 668-74.
- 12 Kitazawa Y, Horie T, Aoki S, Suzuki M, Nishioka K. Untreated ocular hypertension. A long-term prospective study. *Arch Ophthalmol* 1977; **95**: 1180-4.
- 13 Hart Jr WM, Silverman SE, Trick GL, Nesher R, Gordon MO. Glaucomatous visual field damage. Luminance and color-contrast sensitivities. *Invest Ophthalmol Vis Sci* 1990; **31**: 359-67.
- 14 Henson DB, Dix SM, Osborne AC. Results of Friedmann Visual Field Analyser Mark II. Part 1. Results from a normal population. *Br J Ophthalmol* 1984; **68**: 458-62.

Eleven years' experience with retinopathy of prematurity: visual results and contribution of cryoablation

Ilana Nissenkorn, Isaac Ben Sira, Israel Kremer, Dan D Gaton, Rachelle Krikler, Eliahu Wielunsky, Paul Merlob

Abstract

We report our 11 years' experience of cryotherapy for retinopathy of prematurity (ROP). Charts of 624 infants weighing under 1250 g who were admitted to our Neonatal Intensive Care Unit during 1977-87 were reviewed. Three hundred and eighty nine babies survived, and the total ROP prevalence was 57.5%. Cryotherapy was applied to 35%. Only one case (0.25%) of blindness was detected, and four babies (1%) had a final visual acuity of less than 20/200 in one eye. The complication rate following cryoablation was very low.

Accumulating evidence indicates that retinopathy of prematurity (ROP) is a multifactorial disease, the prevention of which is probably impossible even now with advanced methods of blood-gas monitoring and oxygen restriction.¹⁻⁴ Unfortunately it has reappeared as one of the leading causes of childhood blindness, undoubtedly owing to the increased survival of extremely small babies in modern neonatal intensive care units (NICU).^{3,7,8} During the past two decades cryoablation has been more commonly used for the treatment of the acute stages of ROP.^{6,9-10} Following the results of the International Multicenter Study of ROP the treatment of both affected eyes has been recommended.¹⁰ We hereby present our 11 years' experience with the treatment of ROP by cryotherapy.

Patients and methods

Review of the charts of the 624 infants with a birth weight of up to 1250 g who were under the care of our NICU from January 1977 to April 1987 revealed that, among the 389 babies who survived, 224 developed ROP, 79 of whom underwent cryoablation (Tables 1 and 2). Among the 224 infants found to have ROP 115 had a birth weight of less than 1000 g, whereas 109 had a birth weight of 1000 to 1250 g: ROP was present in 79.3% of the former group and in 44.6% of the latter group (Table 2).

Cryoablation was done when confluent fibrovascular proliferations (stage 3 - moderate) occupied more than 3 clock hours in zone I and II with 'plus disease' according to the new classification,^{11,12} and in active stage 3 with reference to the old classification of ROP.¹³ The cryotherapy was performed according to a previously published protocol.¹⁴ However, in five babies the cryotreatment was performed late in the course of the disease, at stage 4-a and b. One baby was

treated in both eyes and four babies in one eye. All these children have remained under regular follow-up, the duration of which ranged from three to 11 years.

The fundoscopic findings of all the ROP patients who were treated during 1977-84, when the old classification was in use, were reclassified by us according to the new classification^{11,12} and evaluated accordingly. The final best corrected visual acuity was examined in all children up to the age of 5 years by the Ffooks symbols test and in children older than this age, by the standard Snellen visual acuity chart. All children underwent cycloplegic refraction (streak skiascopy) and orthoptic evaluation every six months and were given full optical correction according to their last refraction.

Results

Cryoablation was carried out on 79 infants (35.3% of the total). These infants included 56 of the 115 babies (48.7%) weighing below 1000 g and 23 of the 109 infants (21.1%) weighing from 1000 to 1250 g at birth (Table 2).

The visual results are presented in Tables 3 and 4. We detected only one case (0.25%) of bilateral blindness (no perception of light), four eyes (1%) of four babies with a visual acuity of <20/200, and 20 infants (5.14%) with a visual acuity of more than 20/80 in both eyes (Table 3). The five babies with a visual acuity of either no perception of light or <20/200 were treated in stage 4. Among the total population of neonates 364 (93.5%) had normal vision (>20/30) (Tables 3 and 4). There were no major intraoperative or postoperative complications among those undergoing cryotherapy in stage 3 (moderate). During the whole period of follow-up no case of late detachment has been observed.

Table 1 Beilinson premature babies' survival rate, 1977-87

Birth weight (g)	No of children	No of children survived	% Survival
<1000	324	145	44.7
1000-1250	300	244	81.3
Total <1250	624	389	62.3

Table 2 Incidence of ROP among survivors, 1977-87

Birth weight (g)	No of children	No with ROP	% ROP	No of cryotreated children	% of cryotreated children
<1000	145	115	79.3	56	48.7
1000-1250	244	109	44.6	23	21.1
Total	389	224	57.5	79	35.3

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Table 3 Visual results among 389 survivors (birth weight <1250 g) 1977-1987

Visual acuity	No of babies	% of babies	No of eyes	Present retinal findings
No perception of light	1	0.25	2	ROP stage V (closed funnel)*
20/800-20/200	4	1.0	4	Macular displacement with traction fold*
20/80-20/30	20	5.14	BE*	Myopia, peripheral vitreoretinal changes
>20/30	364	93.6	BE*	None

*Cryotreated at stage 4.

Table 4 Correlation between visual acuity and age

Visual acuity	No of preschool children (<6 years)	No of school children (>6 years)
No perception of light	1	0
20/800-20/200	2	2
20/80-20/30	10	10
>20/30	172	192
Total	185	204

Discussion

A survey on the causes of blindness in Israel, carried out by us seven years ago, revealed that during 1976-81 the main cause of blindness was ROP.⁸ It was obvious that there is direct relationship between the survival rate of very small preterm babies and rate of blindness related to ROP: the higher the survival rate, the higher the rate of blindness.¹⁻⁷

For the treatment of ROP by cryoablation we adopted an approach which was based on early cryotreatment, which means at the stage before 'threshold disease' as defined by the Multicenter Trial of Cryotherapy for ROP.⁹ We diagnosed 'threshold disease' when confluent fibrovascular proliferations were found to occupy more than 3 clock hours, in zone I and II with 'plus disease'.^{6,14}

According to the results of the Multicenter Trial of Cryotherapy for ROP^{9,10} retinal detachment may occur in as high as 23% of the cryotreated cases. In contrast we found a much lower rate of retinal detachment (1.25%) among the cryotreated babies. It should be pointed out that these cases were all treated late in the course of their disease (in stage 4). In our opinion the main reason for this difference is the fact that our treatment was performed at an earlier stage than 'threshold disease' as defined by the Multicenter Trial of Cryotherapy for ROP.⁹

We are aware that ROP has a high incidence of spontaneous resolution in various stages of various degrees, and therefore the condition in some of our babies would probably have regressed without treatment. However, we maintain that earlier treatment may prevent the high rate of retinal detachment after treatment reported by the Multicenter Trial.^{9,10}

With respect to the rate of blindness found

among our cryotreated babies, Phelps¹⁷ estimated that the rate of blindness due to ROP, among children with a birth weight under 1000 g, is on average 8%. The survival rate of 62% for the neonates weighing at birth up to 1250 g and admitted to hospital in our NICU compares favourably with that of modern neonatal units in other countries.⁸ On the basis of the statistical calculations made by Phelps¹⁷ it may be assumed that without cryotreatment we should have encountered at least 12 cases of bilateral blindness among our whole group of neonates weighing less than 1000 g. In fact, according to our results, among the entire group of neonates only one blind child (0.25%) and another four children with a visual acuity of <20/200 in one eye only were found. Our results do indicate satisfactory visual findings with an extremely low rate of postcryoablation complications. According to the follow-up results presented in this study, we did not find any of the complications following cryoablation described by several authors.^{10,15}

In conclusion, from our protocol and results we consider that cryotreatment of ROP should be undertaken before the development of 'threshold disease,' as defined by the Multicenter Trial of Cryotherapy for ROP,⁹ and we agree with the recent conclusion of this trial¹⁰ that both eyes should be treated when indicated.

- Kalina RE, Karr DJ. Retrolental fibroplasia: experience over two decades in our institution. *Ophthalmology* 1982; 89: 91-5.
- Gunn TR, Aranda JV, Little J. Incidence of retrolental fibroplasia. *Lancet* 1978; i: 216-7.
- Phelps DL. Retinopathy of prematurity: an estimate of vision loss in the United States - 1979. *Pediatrics* 1981; 67: 924-6.
- Campbell PB, Bull MJ, Ellis FD, et al. Incidence of retinopathy of prematurity in a tertiary newborn intensive care unit. *Arch Ophthalmol* 1983; 101: 1686-8.
- Shohat M, Reisman SA, Krikler R, et al. Retinopathy of prematurity: incidence and risk factors. *Pediatrics* 1983; 72: 159-63.
- Ben-Sira I, Nissenkorn I, Kremer I. Retinopathy of prematurity (ROP): review article. *Surv Ophthalmol* 1988; 33: 1-16.
- Phelps DL. Vision loss due to retinopathy of prematurity. *Lancet* 1981; i: 606.
- Nissenkorn I, Wijzenbeek Y, Cohen S, Ben-Sira I. Etiology of blindness in children in Israel in recent years. *Acta Ophthalmologica* 1986; 25: 742-4.
- Committee for Cryotherapy for retinopathy of prematurity. Multicenter trial of cryotherapy for retinopathy of prematurity (preliminary results). *Arch Ophthalmol* 1988; 106: 471-9.
- Committee for Multicenter Trial of Cryotherapy for Retinopathy of Prematurity. Three-month outcome of cryotherapy for retinopathy of prematurity cooperative group. *Arch Ophthalmol* 1990; 108: 195-204.
- Committee for the Classification of Retinopathy of Prematurity. An international classification of retinopathy of prematurity I. *Arch Ophthalmol* 1984; 102: 1130-5.
- Committee for the Classification of Retinopathy of Prematurity. An international classification of retinopathy of prematurity II. The classification of retinal detachment. *Arch Ophthalmol* 1987; 105: 906-12.
- Reese AB, King M, Owens WC. A classification of retrolental fibroplasia. *Am J Ophthalmol* 1953; 36: 1333-5.
- Ben-Sira I, Nissenkorn I, Grunwald E, Yassur Y. Treatment of acute retrolental fibroplasia by cryoablation. *Br J Ophthalmol* 1980; 64: 758-62.
- Greven CM, Tasman W. Rhegmatogenous retinal detachment following cryotherapy in retinopathy of prematurity. *Arch Ophthalmol* 1989; 107: 1017-8.

Effect of partial cryoablation on retinopathy of prematurity

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Abstract

Cryotherapy has been shown to be an effective treatment for retinopathy of prematurity stage 3. It is said to reduce the unfavourable outcome of the disease by 50%. The accepted method of therapy includes ablation of the whole avascular retina from the ridge to the ora serrata. This is achieved by two to three rows of cryoapplications. When 360° cryo treatment is performed, it requires 52 cryo applications. We present our method of cryotherapy which involves only one row of cryoapplications in the avascular retina anterior to the fibrovascular ridge. An average of 25-30 cryoapplications was required for a 360° treatment. The anatomical results in 23 babies are presented. Complete regression of active retinopathy was found in all.

The first reports¹⁻³ of the use of cryotherapy in the control of the proliferative phases of retinopathy of prematurity (ROP) varied in their conclusions regarding the advantages and limitations of this form of treatment.

In 1978 Kingham⁴ published his disappointing clinical results following cryotherapy. In the same year Hindle and Leyton⁵ reported their successful clinicopathological results in the treatment of active ROP by cryotherapy. Their methods of treatment was similar to that used in the previous reports¹⁻⁴ and consisted of direct freezing of the ridge and the adjacent areas anterior and posterior to it by one to two circular rows of cryoapplications.⁵ Hindle and Leyton showed that in most of the treated eyes the ridge disappeared and no cicatrization developed. Keith, using the same direct method of cryoablation of the ridge but not the avascular retina anterior to it, found no beneficial effect.⁶

In contrast to that method of treatment¹⁻⁶ Ben-Sira and colleagues⁷ described an indirect treatment scheme involving cryoablation of the whole avascular retina, while avoiding direct treatment of the ridge and the neovascular growths posterior to it.⁷ Nissenkorn and coworkers reported a clinicopathological case which showed almost complete regression of the disease in the areas posterior to the atrophic chorioretinal cryo scars and low-grade active disease between the scars.⁸ Subsequently additional reports presented encouraging results following the use of the latter indirect method of cryo treatment.⁹⁻¹²

The encouraging preliminary results of the multicentre trial of cryotherapy for retinopathy of prematurity were published in 1988.¹² The method of cryotherapy described included ablation of the whole avascular retina, from the ridge to the ora serrata, while avoiding the ridge itself. It was found that cryotherapy conferred an

approximately 50% reduction in the unfavourable outcome of ROP.¹²

During the last three years we observed that cryotherapy involving ablation only of the avascular retina close to the ridge, by one row of cryoapplications, without reaching the ora serrata, leads to regression of the neovascular growths. We present here the results of this mode of partial cryotherapy performed in the premature babies under our care in the last three years.

Patients and methods

The charts of all premature babies undergoing cryotherapy due to ROP stage 3 from January 1986 to December 1988 were reviewed. All babies had a birth weight of less than 1250 g and gestational age of less than 28 weeks, except for one neonate whose gestational age was 32 weeks (Table 1). These 23 infants were found to have ROP stage 3 (moderate). The treatment was performed in zone I in six infants (12 eyes) and in zone II in 17 infants (32 eyes). The cryoablation was performed differently from our previous treatment protocol, which we applied until 1986.⁷

The cryotherapy was done with a standard retinal probe. One row of contiguous applications were applied to the avascular retina, reaching the anterior edge of the ridge. The rest of the anteriorly located avascular retina was left untreated. The end point of each application was whitening of the retina. A freezing time of 3 to 4 seconds was usually needed to produce the necessary cryo effect in the retina. Treatment of

Table 1 Patients' clinical data

Case	Treated eye	GA (weeks)	BW (g)	Zone of ROP		Extent of ROP		Cryoablation (hours)	
				RE	LE	RE	LE	RE	LE
1	BE	28	690	II	II	12	12	12	12
2	BE	26	790	I	I	12	12	12	12
3	BE	25	680	I	I	12	12	12	12
4	BE	28	670	I	I	12	12	12	12
5	BE	26	700	II	II	8	8	8	8
6	BE	27	750	II	II	7	7	7	7
7	BE	26	680	I	I	12	12	12	12
8	BE	26	670	I	I	12	12	12	12
9	BE	28	700	II	II	6	6	6	6
10	BE	26	770	II	II	6	6	6	6
11	LE	26	870	II	II	-	6	-	6
12	LE	27	900	II	II	-	6	-	6
13	BE	26	870	II	II	6	6	6	6
14	LE	28	750	II	II	-	8	-	8
15	BE	24	720	I	I	12	12	12	12
16	BE	28	580	II	II	6	6	6	6
17	BE	25	860	II	II	6	6	6	6
18	BE	26	810	II	II	6	6	6	6
19	LE	32	900	II	II	-	6	-	6
20	BE	26	930	II	II	6	6	6	6
21	BE	27	950	II	II	12	12	12	12
22	BE	28	950	II	II	6	6	6	6
23	BE	27	1120	II	II	6	6	6	6

GA=gestational age. BW=birth weight.

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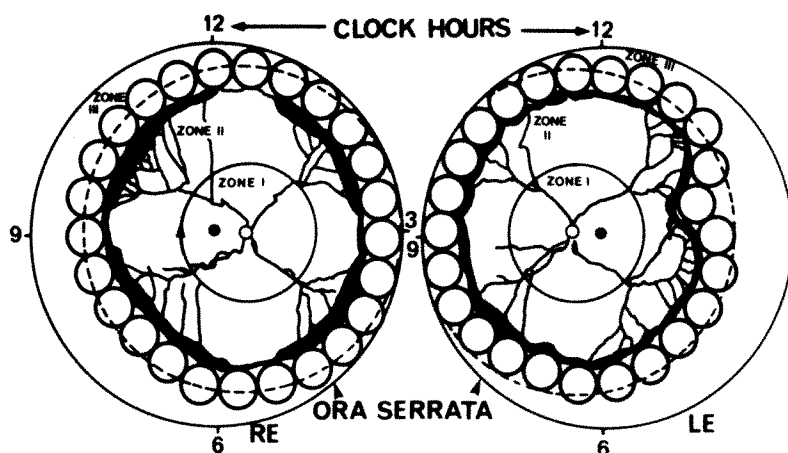


Figure 1 Schematic drawing of partial cryoablation treatment of ROP stage 3, zone II.

the entire circumference of the retina required an average of approximately 25–30 separate treatment spots (Fig 1). In most cases no conjunctival incision was required except for the very small premature babies in whom ROP was located in zone I.

Most of the babies underwent the treatment with topical anaesthetic drops (oxybuprocaine 0.4%), while a neonatologist was in attendance. Six of the neonates who had vasoproliferative disease in zone I (cases 2, 3, 4, 7, 8, 15, Table 1) were treated under general anaesthesia. In those patients a conjunctival incision 3–4 mm in length was made in each quadrant, a cataract cryoprobe was inserted, and one row of cryoapplications was applied throughout 360° in zone I. Post-operatively, 1 drop of atropine 0.5% and dexamethasone 1% were instilled three times a day for one week.

The infants underwent weekly examinations in the first month after treatment, followed by monthly examinations in the following three months, and once every six months thereafter. All infants underwent orthoptic evaluation and retinoscopy until 1 year of age.

Results

In most of the infants the disease was found to be symmetrical, and both eyes were treated with cryoablation (Table 1). The cryotherapy was performed at an average age of 6–12 weeks. In six infants with zone I disease the cryoablation was performed in both eyes throughout the whole retinal circumference (12 clock hours) (Table 1). Thirteen infants with bilateral zone II disease received cryotherapy extending from 6 to 12 clock hours in both eyes (Table 1). Four infants with asymmetrical disease had cryoablation performed in zone II in one eye only, for 6 clock hours (Table 1).

One week after cryoablation the dilatation and tortuosity of posterior pole vessels decreased, and two to four weeks later the active retinal and extraretinal vasoproliferations disappeared in the majority of the cases. In three cases with zone I disease where the cryoapplication did not reach the anterior edge of the ridge we had to add a few cryoapplications closer to the ridge, after which the regression occurred. The results of the two-year follow-up after cryotherapy based on fundus examination revealed total regression of

the active vasoproliferative disease. Atrophic pigmented chorioretinal scars were found anterior to the equator in 70% of the babies and posterior to the equator in 30%. No child developed retinal detachment.

The results of orthoptic evaluation, refraction, and visual acuity testing will be reported in the future.

Discussion

Animal studies have shown that the developing retinal vasculature responds in a biphasic way: (a) initial vasoconstriction and vaso-obliteration in the presence of raised arterial oxygen levels, and (b), on return to room air, by peripheral retinal ischaemia with consequent neovascular proliferation, possibly due to secretion of a vasoproliferative substance by the ischaemic retina.^{13–15} Taylor *et al*¹⁶ have shown that a vasoproliferative factor is released under these conditions. In 1984 Kretzer *et al*¹⁷ described a theory for the induction of ROP according to which a high level of oxygen may trigger extensive gap junction formation between the spindle cells of the avascular vanguard retina, located close to the rearguard zone. Therefore it may be assumed that the development of ROP is triggered by a vasoproliferative substance produced in the ischaemic vanguard retina, as happens in other ischaemic retinopathies.^{18,19} The greater the stimulus in the area of the ischaemic retina to produce this substance, the greater the vasoproliferation, as for example in zone I retinopathy or Rush type ROP.²⁰ As in other ischaemic retinopathies, destruction of the ischaemic tissue is believed to reduce the formation of this vasoproliferative factor and to arrest the vasoproliferative disease.^{21,22} The main question confronting us since we started to perform cryotherapy in active stage 3 ROP is how much avascular retina should be ablated. Between 1976 and 1983 we have been cryoablating the whole avascular retina, avoiding the ridge itself and the neovascular growths, according to a protocol which was described by Ben-Sira *et al*.^{7,23} Since 1986 we have changed the method of cryoablation by which the cryoapplications were performed only anterior to the ridge on the avascular retina, in one row. The rationale for this partial cryotherapy was that the main stimulus for neovascularisation is probably located in the avascular retina adjacent to the ridge, where the metabolic activity of the spindle cells is highest and where one can also find increased numbers of gap junctions.¹⁷ This method has proved to be successful in conferring regression of the neovascular proliferations posterior to the ridge, in all the above presented premature babies. No serious postoperative complications such as rhegmatogenous retinal detachment were noted.²⁴

Therefore we are of the opinion that the treatment, to begin with, in a baby with ROP stage 3 should be partial cryoablation consisting of one or a maximum of two rows of cryoapplications in the avascular retina close to the ridge. The treatment must be done in a confluent pattern close to the ridge, and one must avoid gaps between the cryoablation spots (Fig 1).

- 1 Payne J, Patz A. Treatment of acute retrolental fibroplasia. *Trans Am Acad Ophthalmol* 1972; 76: 1234-46.
- 2 Harris GS. Retinopathy of prematurity and retinal detachment. *Can J Ophthalmol* 1976; 11: 21-5.
- 3 McCormick AQ. Retinopathy of prematurity: current problems. *Pediatrics* 1977; 7: 11-2.
- 4 Kingham JD. Acute retrolental fibroplasia II. Treatment by cryosurgery. *Arch Ophthalmol* 1978; 96: 2049-53.
- 5 Hindle NW, Leyton J. Prevention of cicatricial retrolental fibroplasia by cryotherapy. *Can J Ophthalmol* 1978; 13: 277-82.
- 6 Keith CG. Visual outcome and effect of treatment in stage III developing retrolental fibroplasia. *Br J Ophthalmol* 1982; 66: 446-9.
- 7 Ben Sira I, Nissenkorn I, Grunwald E, Yassur Y. Treatment of acute retrolental fibroplasia by cryopexy. *Br J Ophthalmol* 1980; 64: 758-62.
- 8 Mousel DK. Cryotherapy for retinopathy of prematurity. *Ophthalmology* 1985; 92: 375-8.
- 9 Nissenkorn I, Kremer I, Ben-Sira E, Cohen S, Garner A. A clinicopathological case of retinopathy of prematurity (ROP) treated by peripheral cryopexy. *Br J Ophthalmol* 1984; 68: 36-41.
- 10 Tasman W. Management of retinopathy of prematurity. *Ophthalmology* 1985; 92: 995-9.
- 11 Tasman W, Brown GC, Schaffer DB, et al. Cryotherapy for active retinopathy of prematurity. *Ophthalmology* 1986; 93: 580-5.
- 12 Cryotherapy for retinopathy of prematurity cooperative group. Multicenter trial of cryotherapy for retinopathy of prematurity: preliminary results. *Arch Ophthalmol* 1988; 106: 471-9.
- 13 Ashton N, Ward B, Serpell G. Role of oxygen in the genesis of retrolental fibroplasia: a preliminary report. *Br J Ophthalmol* 1953; 37: 513-20.
- 14 Patz A, Eastham A, Higginbotham DH, Kleh T. Oxygen studies in retrolental fibroplasia II. The production of microscopic changes of retrolental fibroplasia in experimental animals. *Am J Ophthalmol* 1953; 36: 1511-22.
- 15 Ashton N, Ward B, Serpell G. Effect of oxygen on developing retinal vessels with particular reference to the problem of retrolental fibroplasia. *Br J Ophthalmol* 1954; 38: 397-432.
- 16 Taylor CM, Weiss JB, Kistum RD, Garner A. Effect of O₂ tension on the quantities of procollagenase activating angiogenic factor present in the developing kitten retina. *Br J Ophthalmol* 1986; 70: 162-5.
- 17 Kretzer FL, Mehta RS, Johnson AT, Hunter DG, Brown ES, Hittner HM. Vitamin E protects against retinopathy of prematurity through action on spindle cells. *Nature* 1984; 309: 793-5.
- 18 Foos RY. Acute retrolental fibroplasia. *Graefes Arch Clin Exp Ophthalmol* 1975; 195: 87-100.
- 19 Ben-Sira I, Nissenkorn I, Kremer I. Retinopathy of prematurity: major review. *Surv Ophthalmol* 1988; 33: 1-16.
- 20 Nissenkorn I, Kremer I, Kilad E, Cohen S, Ben-Sira I. Rush-type retinopathy of prematurity - a report on four cases. *Br J Ophthalmol* 1987; 71: 559-62.
- 21 Tasman LN, Magargal L, Augsburger JJ. Effects of argon laser photocoagulation on rubeosis iridis and angle neovascularisation. *Ophthalmology* 1980; 87: 400-2.
- 22 May DR, Bergstrom TJ, Parmer AJ, Schwartz JG. Treatment of neovascular glaucoma with transcleral panretinal cryotherapy. *Ophthalmology* 1980; 87: 1106-11.
- 23 Ben-Sira I, Nissenkorn I. Treatment of acute retrolental fibroplasia with cryotherapy. In: McPherson AR, Hittner HM, Kretzner FL, eds. *Retinopathy of prematurity - current concepts and controversies*. Toronto, Philadelphia: Decker, 1986: 129-41.
- 24 Greven CM, Tasman W. Rhegmatogenous retinal detachment following cryotherapy in retinopathy of prematurity. *Arch Ophthalmol* 1989; 107: 1017-8.

Ocular manifestations of onchocerciasis in a rain forest area of West Africa

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Abstract

The epidemiology and natural history of onchocerciasis and its ocular complications in rain forest areas are poorly understood. The present study was conducted on a rubber plantation in a hyperendemic area in the rain forest of Liberia, West Africa, where 800 persons were examined. The prevalence of infection was 84% overall 29% had intraocular microfilariae, and 2.4% were blind in one or both eyes. Onchocerciasis was the cause of all binocular blindness and one-third of all visual impairment. Over half of the visual impairment caused by onchocerciasis was due to posterior segment diseases. Chorioretinal changes were present in 75% of people, and included intraretinal pigment clumping in 52% and retinal pigment epithelium atrophy in 32%. Atrophy of the retinal pigment epithelium was associated with increasing age and severity of infection. Intraretinal pigment was strongly associated with anterior uveitis. There was a strong correlation between uveitis and the inflammatory chorioretinal sequelae: retinitis, intraretinal pigment, subretinal fibrosis, and optic neuropathy. These findings indicate that considerable visual impairment associated with rain forest onchocerciasis is common and is due largely to chorioretinal disease.

Onchocerciasis is a major public health problem in equatorial West Africa.¹ Furthermore, mortality in blind adults is, on average, three to four times greater than of people of the same age who can see.² Although much has been learned about the systemic manifestations of the disease and the ocular changes in the anterior segment, especially in savanna areas,^{3,4} relatively little is known about the epidemiology and natural history of the ocular complications in rain forest areas of West Africa.

While onchocerciasis has been known to exist in Liberia since 1926,⁵ the importance of its ocular sequelae was not initially appreciated. A small study in 1955⁶ found little evidence for severe ocular disease and reported a prevalence of infection of 40%, with 10% of patients having ocular involvement. Another report in 1958 found a prevalence of infection of 69%, but no cases of blindness or obvious lesions due to onchocerciasis were found despite slit-lamp examination.⁷ Another study reported that 49% of adults infected with *Onchocerca volvulus* had microfilariae in the lateral canthus of the eye, an indicator of ocular involvement.⁸ Subsequent studies, however, have indicated that onchocerciasis is an important blinding disease in Liberia. In 1973, Frentzel-Beyme found significant ocular onchocerciasis and a blindness rate of

1.2% in the Bong Range.⁹ This was double the rate found in areas of Liberia free of onchocerciasis. In 1978 Connor and coworkers reported chorioretinitis in 22% and a blindness prevalence of approximately 1% in northern Liberia.¹⁰ Chorioretinitis has also been reported in a high proportion of patients studied in clinical trials in Liberia.¹¹

We undertook a more detailed ocular survey of a population in a hyperendemic area of Liberia to provide further information on the epidemiology and natural history of anterior and posterior segment ocular disease in Liberia and on risk factors associated with those chorioretinal changes.

Materials and methods

CENSUS AND SAMPLING

Employees and their dependants on the Liberian Agricultural Company (LAC) Rubber Plantation in Grand Bassa County, Liberia, were chosen as the study population. A house-by-house census of 1997 people in 18 camps was taken, and the offer of participation in a clinical trial was made. A census card recording name, house, camp, age, sex, tribe, and occupation was completed for each person aged 12 years or more. Participants generally, lived within walking distance of the examination clinic, though transport was available when needed.

EXAMINATION PROCEDURE

Uncorrected and corrected visual acuity was tested by illiterate E chart at 6 m. If either acuity was <6/12, it was assessed with a pinhole. The visual fields were tested with a clear dome Good-lite perimeter with fibre optic target. Fields were recorded as normal, 40-20°, 20-10°, <10° residual field, or absent.

Before anterior segment examination with a Topcon SL5D slit-lamp the patient was positioned in the head-down position for at least two minutes. Then the number of live microfilariae in the anterior chamber was counted (MfAC).

On the basis of presence and extent of flare and cells in the anterior chamber, uveitis was graded as absent, mild, moderate, or severe. The numbers and locations of live and dead microfilariae and punctate opacities in the cornea were recorded. Limbitis was diagnosed by the presence of limbal vessel dilatation, limbal oedema, or white globular opacities. The severity of limbitis was graded as absent, mild, moderate, or severe. Sclerosing keratitis was graded as absent, limbal haze, stroma opacified, or vascularised in the nasal or temporal meridian,

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with or without confluence inferiorly, or completely covering the pupil. Intraocular pressure was measured on all patients over 30 years old with a Goldmann applanation tonometer. The remainder of the anterior segment structures were examined by the slit-lamp, and any other abnormalities were recorded.

After pupil dilatation with 1% tropicamide and 10% phenylephrine, direct and indirect ophthalmoscopy was performed, and fundal abnormalities were recorded. Colour photographs were taken of the Diabetic Research Study fields 1, 2, 3, and 8 (nasal to disc) with a Topcon FE fundus camera.¹² Subsequently the photographs were evaluated in a masked fashion with patient identity obscured. The chorioretinal changes were graded according to the presence and extent of retinal pigment epithelium atrophy, intraretinal pigment clumping, shiny and white intraretinal deposits, retinitis, subretinal fibrosis, and optic neuropathy (neuritis or atrophy); any other abnormalities were also noted.

A medical history was taken, and it included a review of the dermatological, cardiovascular, nervous, and lymphatic systems. A thorough physical examination was also performed with particular reference to the general appearance, location of nodules, lymphadenopathy, dermatological findings, and weight.

Skin biopsies were taken bilaterally with a Holth-type corneoscleral punch from the scapulae, upper buttocks, and calves. These were individually weighed and placed in a flat-bottom microtitre plate well containing 0.1 ml of tissue culture medium (Roswell Park Memorial Institute: RPMI) with penicillin (100 U/ml) and streptomycin (100 µg/mg.) Microfilariae were counted after overnight incubation, and the density of infection was expressed as number per mg of skin (MfS).

DATA ANALYSIS

The analyses included: (1) simple frequency distribution for descriptive analysis; (2) Student's *t* test for comparison between means; (3) χ^2 or Fisher's exact test for comparison of proportions; (4) Pearson's correlation for the computation of bivariate correlation; and (5) multiple regression for computation of the adjusted correlation coefficient.

Results

STUDY POPULATION

A total of 800 persons aged 12 years or more voluntarily reported for detailed physical, parasitological, and ocular examination. The mean camp size was 111, and the mean response rate was 40%. The age and sex distribution of those who were examined was the same as that for the general population, and no obvious sources of selection bias were seen (Table 1).

PREVALENCE AND INTENSITY OF INFECTION

The overall prevalence of infection was 84.3% (Table 2). The prevalence was uniformly high in all age groups and was similar for each sex. It was

Table 1 Age and sex distribution of census and study populations

Age (Years)	Males	Females	Total
Census Population			
12-19	280 (24.5%)	253 (29.6%)	533 (26.7%)
20-29	337 (29.5%)	357 (41.8%)	694 (34.8%)
30-39	281 (24.6%)	185 (21.6%)	466 (23.3%)
40-49	161 (14.1%)	44 (5.1%)	205 (10.2%)
50+	83 (7.3%)	16 (1.9%)	99 (5.0%)
Total	1142 (100%)	855 (100%)	1997 (100%)
Study population			
12-19	146 (28.6%)	95 (32.9%)	241 (30.1%)
20-29	139 (27.2%)	96 (33.2%)	235 (29.4%)
30-39	111 (21.7%)	70 (24.2%)	181 (22.6%)
40-49	84 (16.4%)	20 (6.9%)	104 (13.0%)
50+	31 (6.1%)	8 (2.8%)	39 (4.9%)
Total	511 (100%)	289 (100%)	800 (100%)

Table 2 Prevalence and density of infection by age, sex, and occupation

Total	Number tested	Density positives	Prevalence MF/mg skin	(%)
Total	776*	654	5.3	84.3
Age				
12-19	229	184	4.0	80.4
20-29	231	199	5.1	86.2
30-39	175	145	5.5	82.9
40-49	103	92	8.1	89.3
50+	38	34	8.8	89.5
Sex				
Male	449	424	6.5	85.0
Female	277	230	3.5	83.0
Occupation				
Tapper	215	192	8.6	89.3
Housewife	186	161	4.4	86.6
Student	221	174	3.9	78.7
Other†	154	127	5.0	82.5

*Skin snips from 24 patients were mislaid. †Other occupations included factory workers, drivers, teachers, and nurses.

Table 3 Proportion with monocular or binocular visual impairment by age, sex, and occupation

Total each group	Number 793‡	Blind* 19 (2.4%)	Low Vision† 10 (1.3%)
Age			
12-19	241	2 (0.8%)	4 (1.7%)
20-29	233	6 (2.6%)	2 (0.9%)
30-39	178	1 (0.6%)	2 (1.1%)
40+	141	10 (7.1%)	2 (1.4%)
Sex			
Males	509	8 (1.6%)	7 (1.4%)
Females	284	11 (3.9%)	3 (1.1%)
Occupation			
Tapper	215	4 (1.9%)	3 (1.4%)
Other	578	15 (2.6%)	7 (1.2%)
(Combined)			

*Blind: vision less than 3/60 in one or both eyes. †Low vision: less than 6/18 to 3/60 in one or both eyes. ‡Seven subjects were unable to comprehend the visual acuity test.

significantly higher in those who worked as rubber tappers (89.3%) than in those with an other occupation (<0.02).

Density of infection increased with age, and in males (6.5 microfilariae/mg) it was almost twice that in females (3.5 microfilariae/mg) (Table 2). Tappers were also the most heavily infected occupational group (8.6 microfilariae/mg) with students having the lowest density (3.9 microfilariae/mg).

BLINDNESS AND VISUAL IMPAIRMENT

The rates of blindness and visual impairment increased with age, with the highest rate occurring in people over 40 (Table 3). There were fewer blind males (1.6%) than blind females (3.9%). Although there was less blindness among the tappers (1.9%) than in other occupation (2.6%), more (1.4%) had low vision than did those with other occupations (1.2%).

Table 4 Prevalence of monocular and binocular visual impairment by cause among study population

Cause	Binocular (better eye)		Monocular	
	Blind* Number (%)	Low vision† Number (%)	Blind Number (%)	Low vision Number (%)
Onchocerciasis	3 (0.4)	1 (0.1)	5 (0.6)	1 (0.1)
Glaucoma	0 (0.0)	1 (0.1)	2 (0.3)	0 (0.0)
Cataract	0 (0.0)	1 (0.1)	2 (0.3)	1 (0.1)
Toxoplasmosis	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Trauma	0 (0.0)	0 (0.0)	4 (0.5)	0 (0.0)
Amblyopia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Refractive error	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Other‡	0 (0.0)	1 (0.1)	2 (0.3)	0 (0.0)
Total	3 (0.4)	5 (0.6)	16 (2.0)	5 (0.6)

*Blind: vision less than 3/60. †Low vision: less than 6/18 to 3/60. ‡Other causes include measles, bush medicine, and corneal scarring.

Blindness is the most serious sequel of onchocerciasis, and the three people who were bilaterally blind (vision <3/60 in each eye) all had lesions attributable to onchocerciasis (Table 4). In addition, there were 16 people who were monocularly blind (vision <3/60 in the worst eye), and five of these were blind from onchocerciasis. Seven of those with monocular blindness had some visual impairment (vision <6/18) in the fellow eye. In four of these the visual impairment was due to onchocerciasis lesions. Five subjects (0.6%) had binocular low vision and five (0.6%) had monocular low vision. Thus 29 subjects had visual impairment in one or both eyes. In 9 (31.0%) this was attributed to onchocerciasis, and of those in whom blindness or low vision was due to onchocerciasis it was due to anterior segment disease in four (40.0%) and to posterior segment disease in six (60.0%).

ANTERIOR SEGMENT FINDINGS

MfAC were present in 191 (23.9%). The prevalence of microfilariae in the anterior chamber increased with age for both males and females (Fig 1). Live and dead microfilariae (MfC) were present in 13.6% of the population overall, but, except for an apparent increase in elderly women, there was less of an increase with age (Fig 2). The proportion of those with punctate corneal opacities was 19.1% overall, with no clear age or sex dependency, but again there was an increase

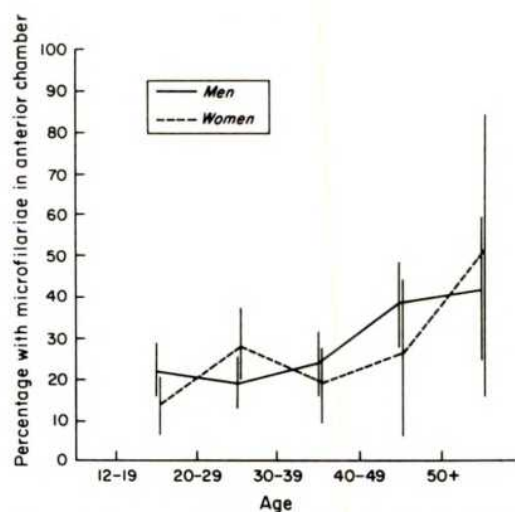


Figure 1 Proportion and 95% confidence limits of those with microfilariae in the anterior chamber.

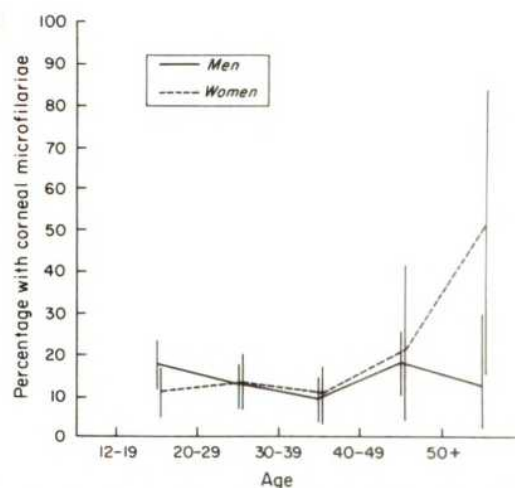


Figure 2 Proportion and 95% confidence limits of those with microfilariae in the cornea.

in prevalence in the older women (Fig 3). Sclerosing keratitis had an overall prevalence of 5% and was more common in the older subjects (Fig 4).

POSTERIOR SEGMENT FINDINGS

Chorioretinal changes were present in 596 (76.2%) of 782 subjects with readable fundus photographs (Fig 5-11). The commonest change was intraretinal pigment (IRP), which occurred in 405 patients (51.8%), while retinal pigment epithelium atrophy was found in 251 (32.1%). Less common were white intraretinal deposits in 168 (21.4%) and shiny intraretinal deposits in 79 (10.1%) of the patients (Table 5). On univariate analysis atrophy of retinal pigment epithelium was correlated with age, MfC, punctate corneal opacities, total number of nodules, MfS, sclerosing keratitis, and being a tapper. Age and MfC remained significantly correlated in multivariate analysis after controlling for other risk factors ($p < 0.05$). Subretinal fibrosis and optic neuropathy were both associated with increasing age. Subretinal fibrosis, optic neuropathy, IRP, and retinitis were all associated with uveitis, and the correlation persisted for IRP and retinitis after multivariate analysis. IRP was also found in those with MfAC and a skin rash. Retinitis was

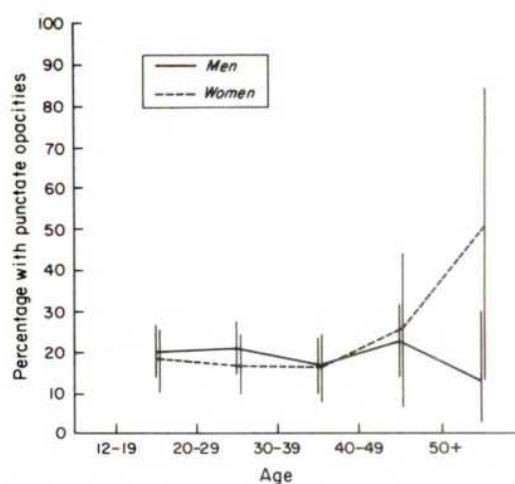


Figure 3 Proportion and 95% confidence limits of those with punctate opacities in the cornea.

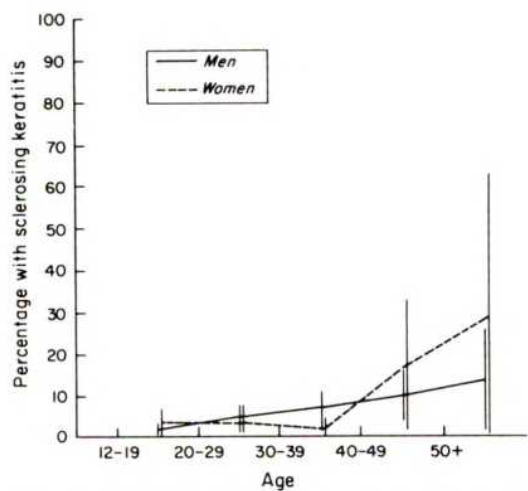


Figure 4 Proportion and 95% confidence limits of those with sclerosing keratitis.

associated with prior treatment with diethyl-carbamazine and with limbitis. White and shiny intraretinal deposits were weakly correlated with punctate opacities in the cornea.

All the people were classified on clinical and parasitological findings as to the overall likelihood of their actually having onchocerciasis. It should be remembered that they lived in an endemic area and were highly likely to have been exposed, if not infected. Those who had microfilariae in either the skin or the eye were classified as having definite onchocerciasis; those without skin or ocular microfilariae but who had punctate corneal opacities, sclerosing keratitis, characterstic nodules, a history of previous treatment, or who had skin lesions consistent with onchodermatitis were classified as having probable onchocerciasis. People in whom all of the above criteria were negative were considered not to have onchocerciasis. Subretinal fibrosis and optic neuropathy were found only in those with definite onchocerciasis; retinitis, limbitis, and uveitis were found in those in the definite or probable groups (Table 6). Interestingly, atrophy



Figure 6 Severe chorioretinitis and intraretinal pigment clumping in a 19-year-old male with a mean skin snip count of 15 Mf/mg.

of retinal pigment epithelium was common in each group but more prevalent in those patients with definite or probable onchocerciasis.

There was no correlation between onchocerciasis status and either age or sex, though a higher proportion of rubber tappers had onchocerciasis.

Discussion

Onchocerciasis was the main cause of bilateral blindness in this population. We found a high prevalence of ocular involvement and in particular a high prevalence of posterior segment changes. The examinations were in part carried out as a preliminary screen for clinical trial.^{13 14} This may have introduced some bias, as it is possible that those who considered themselves healthy might see little purpose in participating. Indeed, we ascertained by interview that the requisite blood samples and skin biopsies were deterrents to participation for at least some people.

We found a prevalence of infection of 84%. This is higher than in a previous study in the area in 1975, which reported a prevalence of infection of only 63%,¹⁵ but they took fewer skin snips. During the past 10 years there have been important changes in this area associated with the progressive development of the plantation,

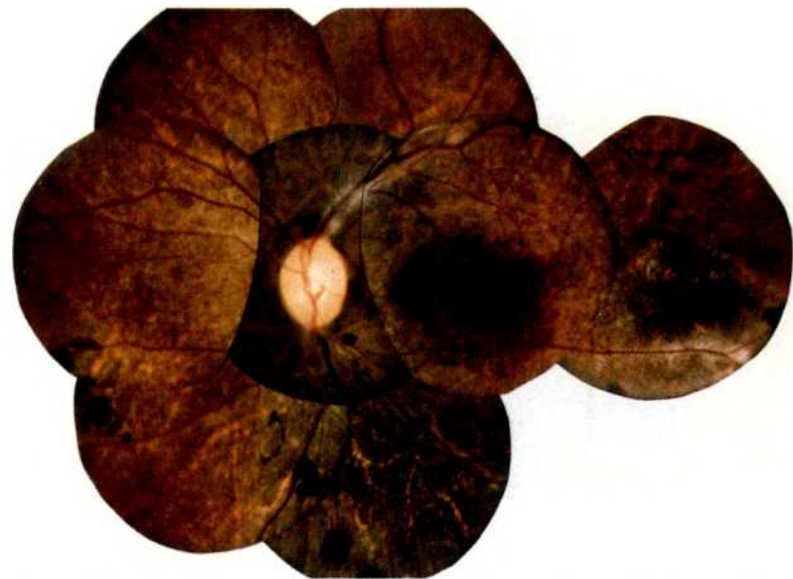


Figure 5 Montage of fundus showing discrete areas of retinal pigment epithelium atrophy (RPEA) and areas of RPE hypertrophy in a 19-year-old male with a mean skin snip count of 17 Mf/mg.

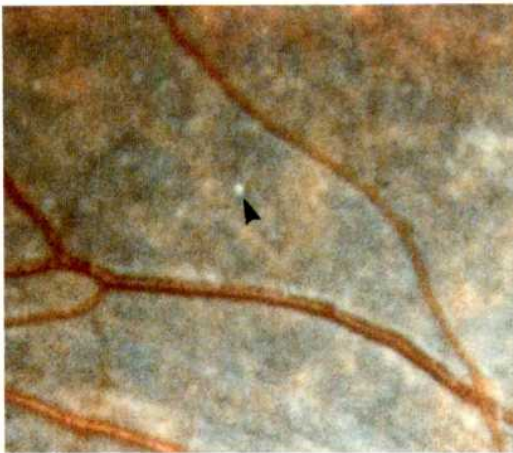


Figure 7 A shiny white deposit (arrow).

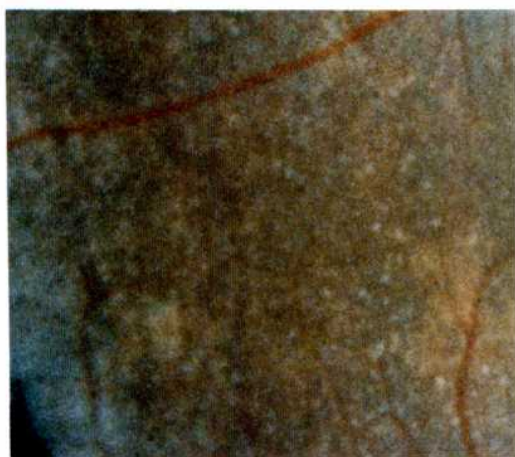


Figure 8 Multiple white intraretinal deposits temporal to the macula in a 19-year-old male with a mean skin snip count of 17 Mf/mg.

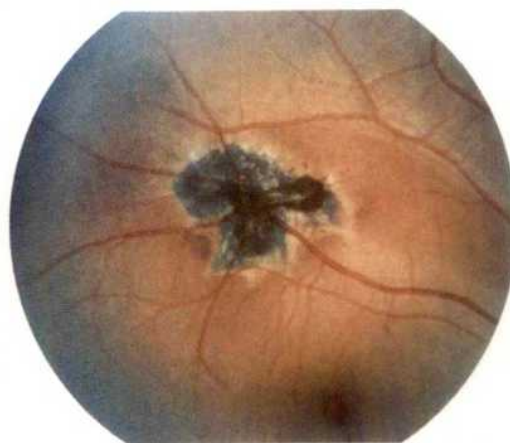


Figure 10 Area of subretinal fibrosis with overlying pigment in a 17-year-old male patient with a mean skin snip count of 6 Mf/mg.

which requires the recruitment of new workers, many of whom came from other hyperendemic areas.

The density of infection was especially high in males and tappers, who were also at higher risk of infection than other occupations. The tappers, who are mostly male, work among the rubber trees near the breeding sites and are more exposed to the biting black flies that transmit onchocerciasis. Their clothing, often minimal, offers little protection from the flies. It is interesting that there was not a correspondingly high proportion of blind tappers. Almost paradoxically, it was the elderly females who had the highest rate of blindness. This may be because tappers leave the plantation when their vision is so badly affected that they are no longer able to work. On the other hand the wives or female relatives of sighted male employees would remain for as long as their husbands worked, and this would artificially increase the numbers of visually impaired females.

The prevalence of bilateral blindness was also relatively low (0.4%) but it was all attributable to onchocerciasis. This rate is still twice that of most developed countries.¹⁶ In other studies in rain forest areas, Anderson *et al* reported a 2.0% blindness rate from all causes in the Cameroon rain forest, three-fourths of which was due to onchocerciasis.¹⁷ In Liberia, Frentzel-Beyme

reported a 1.2% blindness rate among 285 persons in a rural area,⁹ with the majority of blindness due to onchocerciasis. From a larger survey he later reported a 1.9% prevalence of blindness, with one-fourth attributable to onchocerciasis.¹⁸

The presence of microfilariae in the anterior chamber (MfAC) is often taken as a measure of ocular disease in onchocerciasis, but the validity of this as an indicator is limited by the relative difficulty in obtaining reproducible data unless the examination technique is standardised.¹⁹ Prevalence figures for MfAC from various studies in Liberia show considerable differences for the data we report. Connor and coworkers found microfilariae in the anterior chamber in about 41% of their subjects,¹⁰ while Frentzel-Beyme reported a prevalence of only 8.7%.⁹ This lower figure is almost certainly due in part to the fact that the patients were examined without previous positioning with the head down.

In the present study, as in the Cameroon rain forest,²⁰ older women had a higher prevalence of corneal microfilariae and punctate opacities. Perhaps this is because the older women remain in the population longer, but hormonal factors have also been implicated. Anderson and coworkers suggest that a protective role is played by hormonal factors in females during their reproductive years.²⁰

The prevalence of sclerosing keratitis was higher in our Liberian study (5%) than the 1.6%

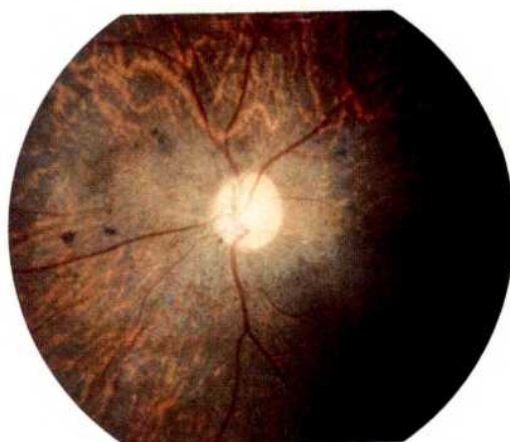


Figure 9 Advanced retinitis, IRP, RPEA, and optic atrophy in a 30-year-old female with a mean skin snip count of 111 Mf/mg.

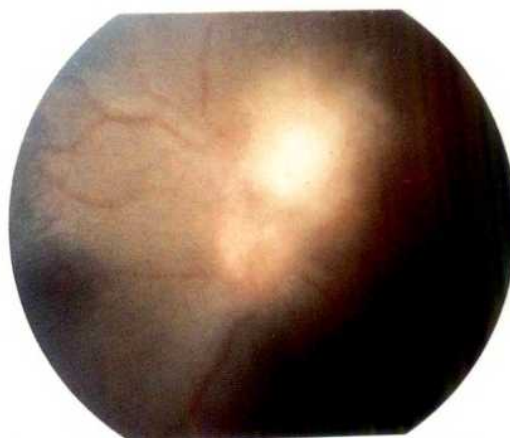


Figure 11 Large area of acute retinitis in a 14-year-old patient with a mean skin snip count of 9 Mf/mg.

Table 5 Univariate and multivariate analysis of fundus abnormalities

	RPEA†	Subretinal fibrosis	Optic neuropathy	IRP‡	Retinitis	White deposits	Shiny deposits
	(251)§ (***)	(8) ***	(8) **	(405) —	(34) —	(168) —	(79) —
Age	—	—	—	—	—	—	—
MFC	(**)	—	*	—	—	—	—
Punctate opacities	**	—	—	—	—	*	*
Nodule total	—	—	—	—	—	**	—
MFS	*	—	—	—	—	—	—
Sclerosing keratitis	*	—	—	—	—	—	—
Occupation tapper	**	—	—	—	—	—	—
Uveitis	—	***	***	(**)	(**)	—	—
MEAC	—	—	—	**	—	*	—
Skin rash	—	—	—	*	—	—	—
Prior treatment	—	—	—	—	*	—	—
Limbitis	—	—	—	—	*	—	—

* $p=0.09$ to 0.05 . ** $p=0.04$ to 0.01 . *** $p<0.01$. () Significant after multivariate analysis, controlling for other risk factors. †Retinal pigment epithelium atrophy. ‡Intraretinal pigment. §Numbers in parentheses are numbers of people with fundus abnormality in one or both eyes.

prevalence found in the Cameroon rain forest.²⁰ Although the early stage of limbal haze was not classified as sclerosing keratitis in the Cameroon study, when Liberian subjects with limbal haze alone were excluded the overall prevalence still remained at 4.2%. Sclerosing keratitis was often seen in a milder form in the Liberian rain forest population than in the savanna, and in this population of largely able-bodied men it was associated with relatively little visual impairment. It was the cause of bilateral blindness in one patient, while secondary glaucoma caused blindness in another.

The advanced chorioretinal abnormalities associated with onchocerciasis have been described in detail,²¹ but little is known about the earlier stages of ocular involvement. A high number of vitreoretinal changes were reported in a study of 30 Liberian men¹¹ who were examined in great detail with direct and indirect ophthalmoscopy, fundus photography, fluorescein angiography, and triple-mirror contact lens examination. Even in the present study, with a somewhat less detailed examination including only indirect ophthalmoscopy and fundus photography, the prevalence of chorioretinal changes was high.

The pathogenesis of the chorioretinal changes in onchocerciasis is not clear, and many theories have been advanced. In 1935 Bryant suggested that the adult worms secrete a systemic toxin which affects the fundus and optic nerve.²² This

type of process would be consistent with the bilateral symmetrical nature of the disease. Bryant also suggested that microfilariae invade the optic tract producing perivascular infiltration and bilateral symptoms.

In 1945 Ridley concluded from his own, and other, observations that dead microfilariae in the choroid cause occlusion of the smaller blood vessels and atrophy of the retina.²³ He also implicated perivascular infiltration and endothelial proliferation of the short ciliary vessels in the production of a diffuse chorioretinal degeneration. In 1955 Budden echoed Bryant's suggestion that posterior segment damage might be due to the effects of toxins released by adult worms.²⁴ A combined effect of these toxins and avitaminosis A was postulated by Rodger,²⁵ whereas Choyce suggested that onchocercal chorioretinitis was only a genetic condition.²⁶ Neumann and Gunders suggested that the chorioretinal lesion was either due to an inflammatory reaction caused by the death of microfilariae in situ in the posterior segment or diffusion of toxic products from disintegrating microfilariae into the choroid and retina.²⁷ Garner suggested that the marked retinal and choriocapillaris atrophy was attributable to a preceding chorioiditis.²⁸

Although the precise mechanism is unknown, the role of systemic immune processes in pathogenesis of some of the complications of onchocerciasis has been established.²⁹⁻³¹ An association between circulating immune complexes and the occurrence of major ocular complications, including chorioretinitis, was reported.³² Furthermore, circulating antibodies against various retinal antigens, including retinal S-antigen have been demonstrated in patients with retinopathy due to onchocerciasis.³³⁻³⁵

Donnelly and coworkers have demonstrated that chorioretinal changes similar to those in the human onchocerciasis occur in a monkey model after the vitreal injection of *O. volvulus* microfilariae.³⁶ They suggested that the changes could be directly related to the presence of microfilariae in the retina. Microfilariae were found in the retina adjacent to the areas of retinal pigment epithelial changes, but with no surrounding inflammation. This would point to either a purely mechanical effect resulting from the passage of microfilariae through the retina or to the effect of toxins released by microfilariae. In their studies there was massive death of microfilariae and possibly an accumulation of microfilarial antigens, producing a change in the host immune status. This in turn could be followed by severe inflammation causing the tissue damage in the retina. Punctate corneal opacities, which are acute inflammatory foci enveloping dead microfilariae, demonstrate a similar chain of events in the anterior segment.

We conducted a risk factor analysis to gain further insight into the pathogenesis of some of the chorioretinal changes. We found a strong correlation between both anterior segment disease (live and dead microfilariae punctate opacities, and sclerosing keratitis) and systemic markers of cumulative disease (age, numbers of skin microfilariae, occupation, and total number of nodules). This suggests that similar

Table 6 Percentage prevalence of fundus abnormalities, ocular findings, and demographic characteristics by onchocerciasis status

	Total number	Onchocerciasis status*		
		Definite	Probable	None
Subretinal fibrosis	8	1%	0	0
Optic neuropathy	7	1%	0	0
Retinitis	34	5%	5%	0
Limbitis/uveitis	20	3%	2%	0
RPEA	248	34%	32%	22%
White deposits	158	21%	20%	22%
Shiny deposits	75	9%	18%	10%
IRP	395	52%	52%	53%
Mean age (years)		28.2	28.7	24.1
Males		66%	66%	59%
Rubber tapper†		21%	9%	3%
Total	756‡	641	44	71

*See text for grounds for classification. †Twenty four people had missing MFS values and 20 had unreadable photographs. ‡ χ^2 test, $p=0.001$.

mechanisms are likely to cause both atrophy of retinal pigment epithelium and the anterior segment changes. The significance of the shiny, white intraretinal deposits seen in patients with onchocerciasis is unclear. These lesions were correlated with punctate opacities and may point to an inflammatory aetiology. It is possible that they represent the retinal equivalent of the corneal lesions and are small focal areas of inflammation surrounding dead or dying microfilariae; it may not be possible to determine their exact nature until further histopathological material is available.

The impact of onchocerciasis in rain forest areas in terms of visual impairment has often been underestimated, but our results suggest it is of considerable importance. Most posterior segment changes in onchocerciasis threaten sight and may cause irreversible damage. Further studies are needed to identify risk factors for chorioretinitis in hyperendemic areas and to treat as early as possible so that some visual loss may be prevented.

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- 1 Prost A. The burden of blindness in adult males in the savannah villages of West Africa exposed to onchocerciasis. *Trans R Soc Trop Med Hyg* 1986; 80: 525-7.
- 2 Prost A, Vaugelade J. La surmortalité des aveugles en zone de savane Ouest-Africaine. *Bull WHO* 1981; 59: 773-6.
- 3 Anderson J, Fitt RL. Ocular onchocerciasis. In: Bulford CH, Connor DH, eds. *Pathology of tropical and extraordinary diseases*. Washington: Armed Forces Institute of Parasitology, 1976; 373-81.
- 4 Anderson J, Fuglsang H. Ocular onchocerciasis. *Tropical Diseases Bulletin* 1977; 74: 257-72.
- 5 Strong RP. *The African Republic of Liberia and the Belgian Congo*. Boston: Harvard University Press, 1930.
- 6 Burch TA, Qualls DM, Greenville HJ. Onchocerciasis in Liberia. *Am J Trop Med Hyg* 1955; 4: 923-9.
- 7 Miller MJ, Franz KN. Some clinical aspects of onchocerciasis in Liberia. *Am J Trop Med Hyg* 1958; 7: 558-60.
- 8 Miller MJ, Gunders AE. Studies on onchocerciasis in Liberia. *Proceedings of the Smith International Congress of Tropical Medicine and Malaria*. Instituto de Medicina Tropical, Lisbon, 1958.
- 9 Frentzel-Beyme R. The prevalence of onchocerciasis and blindness in the population of the Bong Range, Liberia. *Trop Med Parasitol* 1973; 24: 339-57.
- 10 Connor DH, Cupp EW, Ganley JP, Gibson DW, Schiller EL. *Report of studies on onchocerciasis in Northern Liberia, including topical treatment with diethylcarbamazine: pathology, ophthalmology, parasitology, and entomology; and recommendation for control of the disease*. American Public Health Association: 1978.
- 11 Taylor HR, Murphy RP, Newland HS, et al. Treatment of onchocerciasis; the ocular effects of ivermectin and diethylcarbamazine. *Arch Ophthalmol* 1986; 104: 863-70.
- 12 Diabetic Retinopathy Study Research Group. Report No. 6: Design, methods, and baseline results. *Invest Ophthalmol Vis Sci* 1981; 21: 212.
- 13 White AT, Newland HS, Taylor HR, et al. Controlled trial and dose-finding study of ivermectin for treatment of onchocerciasis. *J Infect Dis* 1987; 156: 463-70.
- 14 Newland HS, White AT, Greene BM, et al. The effect of single dose ivermectin therapy on human *Onchocerca volvulus* infection and onchocercal ocular involvement. *Br J Ophthalmol* 1988; 72: 561-9.
- 15 Frentzel-Beyme R. The geographical distribution of *O. volvulus* infection in Liberia. *Trop Med Parasitol* 1975; 26: 70-87.
- 16 World Health Organisation. *Methods of assessment of avoidable blindness*. WHO Offset Publication No. 54. Geneva: World Health Organisation, 1980.
- 17 Anderson J, Fuglsang H, Hamilton PJS, Marshall TFdeC. Studies on onchocerciasis in the United Cameroon Republic II. Comparison of onchocerciasis in rain-forest and Sudan-Savannah. *Trans R Soc Trop Med Hyg* 1974; 68: 209-21.
- 18 Frentzel-Beyme RR. Visual impairment and incidence of blindness in Liberia and their relation to onchocerciasis. *Trop Med Parasitol* 1975; 26: 469-88.
- 19 Thylefors B, Brinkmann UK. The microfilarial load in the anterior segment of the eye. A parameter of intensity of onchocerciasis. *Bull WHO* 1977; 55: 731-7.
- 20 Anderson J, Fuglsang H, Hamilton PJS, Marshall TFdeC. Studies on onchocerciasis in the United Cameroon Republic I. Comparison of populations with and without *Onchocerca volvulus*. *Trans R Soc Trop Med Hyg* 1974; 68: 190-208.
- 21 Bird AC, Anderson J, Fuglsang H. Morphology of posterior segment lesions of the eye in patients with onchocerciasis. *Br J Ophthalmol* 1976; 60: 2-20.
- 22 Bryant J. Endemic retino-choroiditis in the Anglo-Egyptian and its possible relationship to *Onchocerca volvulus*. *Trans R Soc Trop Med Hyg* 1935; 28: 523-32.
- 23 Ridley H. Ocular onchocerciasis, including an investigation in the Gold Coast. *Br J Ophthalmol* 1945; suppl 10.
- 24 Budden FH. Incidence of human infection with onchocerciasis in different communities in relation to the incidence and type of the ocular lesions. *Br J Ophthalmol* 1955; 39: 321-32.
- 25 Rodger FC. Posterior degenerative lesion of onchocerciasis. *Br J Ophthalmol* 1958; 42: 21.
- 26 Choyce DP, IV. Some observations on the ocular complications of onchocerciasis and their relationship to blindness. *Trans R Soc Trop Med Hyg* 1958; 52: 112-21.
- 27 Neumann E, Gunders AE. The posterior segment lesion of ocular onchocerciasis. Histological aspects. *Isr J Med Sci* 1972; 8: 8-9.
- 28 Garner A. Pathology of ocular onchocerciasis: human and experimental. *Trans R Soc Trop Med Hyg* 1976; 70: 374-7.
- 29 Greene BM, Taylor HR, Humphrey RL. Proteinuria associated with diethylcarbamazine treatment of onchocerciasis. *Lancet* 1980; i: 254-5.
- 30 Paghandi R, Ngu JL, Levinsky RJ. Circulating immune complexes in onchocerciasis. *Clin Exp Immunol* 1980; 39: 570-5.
- 31 Steward MW, Sisley B, Mackenzie CD, El Sheikh H. Circulating antigen-antibody complexes in onchocerciasis. *Clin Exp Immunol* 1982; 48: 17-24.
- 32 Greene BM, Taylor HR, Brown EJ, Humphrey RL, Lawley TJ. Ocular and systemic complications of diethylcarbamazine therapy for onchocerciasis: association with circulating immune complexes. *J Infect Dis* 1983; 147: 890-7.
- 33 Newsome DA, Hewitt TA, Quinn TC, et al. Immune status alteration in onchocerciasis, with and without retinopathy. *XXV International Congress of Ophthalmology*. 1986: 4.
- 34 Vintain P, Thillaye B, LeHoang P, Sanite-Landy J, Chanderver J, Faure JP. Sensitivity of patients with ocular onchocerciasis to filarial antigen and retinal autoantigen. *Fourth International Symposium on Immunology and Immunopathology of the Eye* 1986: 51.
- 35 Chan C, Nussenblatt RB, Kim MY, Palestine AG, Awadzi K, Ottesen EA. Immunopathology of ocular onchocerciasis 2: anti-retinal autoantibodies in serum and ocular fluids. *Ophthalmology* 1987; 94: 439-43.
- 36 Donnelly JJ, Taylor HR, Khatami M, et al. Immunopathology of onchocerciasis: ocular disease in monkeys. *Invest Ophthalmol Vis Sci* 1984; 25 (suppl): 188-4.

Closure of leaking filtering blebs with cyanoacrylate tissue adhesive

Alan H Zalta, Richard H Wieder

Abstract

Five leaking filtering blebs, occurring between 10 months and 21 years after trabeculectomy, were closed with cyanoacrylate tissue adhesive. Filtering bleb integrity was preserved in four cases, so that additional microsurgery was avoided. The only problem associated with use of tissue adhesive was the development of corneal abrasions in three cases. Although it is an accepted treatment for these conjunctival fistulas, only nine previous cases have been reported to our knowledge. We strongly recommend the use of tissue adhesive as a presurgical treatment in the management of leaking filtering blebs which present as a late postoperative complication of glaucoma surgery.

A leaking filtration bleb is a serious sight-threatening complication of glaucoma surgery which may lead to hypotony, a flat anterior chamber, cataract, choroidal detachment, macular oedema, failure of the filtration bleb, and endophthalmitis. This complication is routinely managed by pressure patching, medications to reduce aqueous flow, suture repair, wound revision, bandage soft contact lens, scleral shell, collagen shield, and cyanoacrylate tissue adhesive.¹⁻¹⁵ While application of cyanoacrylate tissue adhesive is an accepted treatment for the condition,^{14,15} there have been only nine case reports detailing its effectiveness.¹⁻⁷ To our knowledge the five cases which we describe here represent the largest series of leaking filtering blebs repaired with cyanoacrylate tissue adhesive. We also describe the technique of tissue adhesive application employed.

Materials and methods

These five cases represent all leaking filtering blebs managed by one of the authors (AHZ) within the last five years which occurred as a remote complication of glaucoma surgery. The conjunctival bleb leak was identified and located on Seidel testing by a dramatic change in the colour of applied 2% fluorescein sodium from deep orange to light green. The repair was performed at the surgeon's consulting room under direct visualisation without the use of loupes or a microscope. The patient was placed in a recumbent position and the eye was anaesthetised with topically applied proparacaine. A lid speculum was inserted to prevent lid closure during and after application of the tissue adhesive. The patient was instructed to fixate with the contralateral eye to optimise ocular positioning and to prevent the eyelid from coming into contact with the glue. The eye was positioned

with the wound leak perpendicular to the vertical direction of application so as to prevent mis-application and run-off of the tissue adhesive to other parts of the eye. The conjunctival fistula site was dried with a cotton tip applicator or Weck-cel sponge just prior to application of the tissue adhesive. After securing a 30 gauge needle to a tube of Histoacryl Blue (n-butyl-2-cyanoacrylate) tissue adhesive, one to three drops of tissue adhesive were focally applied to the fistula site. After the tissue adhesive crystallised, the eye was examined at the slit-lamp to ensure proper coverage of the wound leak.

Then, antibiotic and/or antibiotic-steroid ointments were instilled to reduce ocular irritation from the glue. In accordance with the needs of the particular patient the eye was either pressure patched for 24 hours with or without a bandage soft contact lens, treated by ointment instillation every one hour while the patient was awake, or treated with topical antibiotic drops. The site of application of the tissue adhesive was examined the following day for optimal positioning and for presence of the bleb leak by Seidel testing. If the tissue adhesive had become dislodged or if a bleb leak persisted, tissue adhesive was reapplied to the site of leakage.

In using tissue adhesives for this specific purpose we followed some general principles. First, the leakage site was identified at the slit-lamp with a 2% fluorescein sodium solution. Fluorescein sodium strips may further traumatise a compromised and tenuous conjunctival epithelium adjacent to the margins of the wound leak and should be avoided if possible. Secondly, a tiny amount of adhesive was used. Even with a 30 gauge needle one drop of tissue adhesive is sufficient to cover not only the leak site but also 1 to 2 mm of surrounding tissue if optimally applied. Thirdly, the leak site was dried prior to application of tissue adhesive. Bubbles were occasionally seen within the tissue adhesive during crystallisation. These bubbles are believed to be due to the tissue adhesive actively 'walling off' externalised aqueous. Fourthly, run-off or extension of tissue adhesive to surrounding tissues was minimised. Proper ocular positioning and alignment before application of the tissue adhesive is critical. Fifth and lastly, a lid speculum is necessary to prevent adherence of the eyelid to the conjunctiva and to prevent blinking while the tissue adhesive is crystallising.

Case reports

CASE 1

A 53-year-old black female with advanced primary open-angle glaucoma in the left eye, controlled by a trabeculectomy performed in

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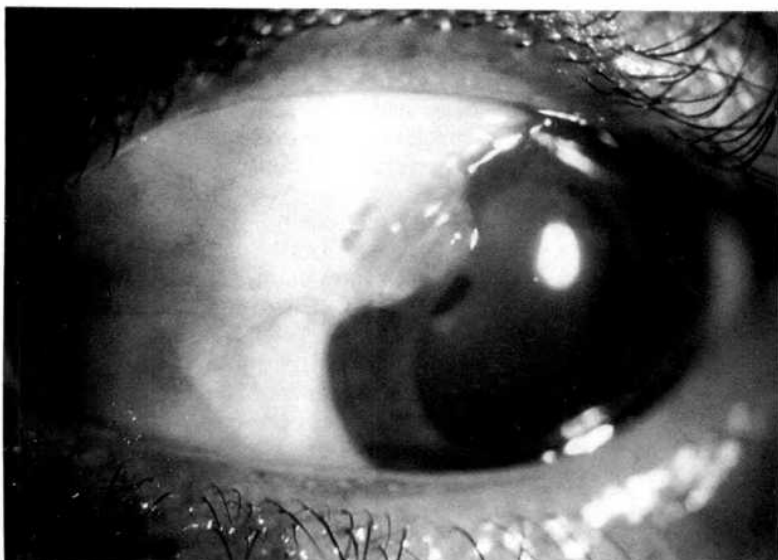


Figure 1 Large multicystic glaucoma filtering bleb with healed conjunctival fistula on the overhanging corneal margin after removal of tissue adhesive.

1971, developed a spontaneous leak of the filtering bleb in 1985. On initial examination a Seidel-positive wound leak was noted through the corneal edge of an overhanging, large, multicystic, superonasal filtering bleb (Fig 1). The intraocular pressure by applanation tonometry was 14 mmHg. The anterior chamber was deep and quiet. Tissue adhesive was applied to the fistula site and the eye was pressure patched over Polysporin (polymyxin B-bacitracin) ointment. On examination the next day the tissue adhesive was in a good position overlying the wound leak, and a Seidel test was negative. The eye was pressure patched again over polymyxin B-bacitracin ointment. On the second day after treatment the glue had become dislodged from the fistula site into the medial cul-de-sac. The site of the wound leak was covered by conjunctiva and a Seidel test was negative. The fistula has subsequently remained closed. A corneal epithelial defect was present adjacent to the healed fistula. This iatrogenic abrasion resolved after pressure patching for three more days. The intraocular pressure was 13 mmHg the day after application of the tissue adhesive and has remained in the low teens without further treatment.

CASE 2

A 60-year-old black male with end-stage primary open-angle glaucoma in his only eye, the right eye, controlled by a trabeculectomy performed in October 1987 developed a spontaneous leak in the filtering bleb in October 1988. On examination the intraocular pressure by applanation tonometry was 4 mmHg. A Seidel-positive wound leak was noted from a thin walled, posterior superotemporal filtering bleb. The anterior chamber was deep and quiet. Tissue adhesive was applied to the fistula site, but the eye was not pressure patched because of a blind fellow eye with no light perception. Tobramycin eye drops, one four times a day, were started. The next day the tissue adhesive was no longer

in place, the intraocular pressure was 6 mmHg, and there was a persistent Seidel positive wound leak. Tissue adhesive was reapplied and the eye was pressure patched over Cortisporin polymyxin B-bacitracin-neomycin-hydrocortisone ointment. The next day the glue was still in place, the intraocular pressure was 9 mmHg, and the site of the wound leak was Seidel negative. Pressure patching was repeated daily for four more days. When the tissue adhesive was removed two days later the conjunctiva had healed over the wound leak and a Seidel test was negative. The conjunctival fistula has subsequently remained closed. A corneal epithelial defect was present where the tissue adhesive had extended from the leaking bleb on to the cornea. The iatrogenic abrasion resolved after pressure patching for two more days. The intraocular pressure increased to 19 mmHg three weeks after the wound leak had sealed, but has been controlled in the low teens since that time with the addition of timolol eye drops 0.5% twice a day.

CASE 3

A 55-year-old black female with end-stage primary open-angle glaucoma in the right eye controlled by a trabeculectomy in 1967 developed a leaking filtering bleb in 1988 during treatment for haemophilus conjunctivitis. Despite two weeks of topical and intravenous antibiotics the filtering bleb flattened, opacified, and developed a Seidel-positive fistula which did not close with several days of pressure patching.

On initial examination there was a Seidel-positive wound leak in a small cystic bleb overhanging the superior limbus and an intraocular pressure of 20 mmHg while the patient was using timolol 0.5% twice a day and methazolamide 50 mg by mouth twice daily. There was no infiltrate in or around the filtering bleb and the anterior chamber was deep. Topical tobramycin twice daily and prednisolone acetate 1% four times a day were being used. Tissue adhesive was applied to the wound leak site, and the eye was pressure patched over polymyxin B-bacitracin ointment. Over the next three days tissue adhesive was reapplied to the leak site twice more. By the fifth day the fistula was closed and was Seidel-negative. However, the intraocular pressure increased to the mid-20s mmHg, requiring the addition of pilocarpine eye drops four times a day. On the eighth day a minute wound leak, with a delayed positive Seidel test by 3 to 4 seconds, was present on the edge of the glue. Tissue adhesive was applied to the new leak site, and the eye was pressure patched over Cortisporin ointment. Two days later the leak site remained Seidel-negative, and topical medications were reinstituted. Over the next five weeks the intraocular pressure slowly increased into the mid-30s mmHg despite maximum ocular hypotensive therapy. Six weeks after the last application of tissue adhesive, the crystallised glue was removed from the closed fistula site, and a new trabeculectomy with bleb revision was performed. The intraocular pressure was 9 to 10 mmHg when the patient was on no ocular hypotensive medication for the six months following surgery.

CASE 4

A 77-year-old white female with angle closure glaucoma in the right eye controlled by a Scheie procedure performed in 1984 developed a wound leak in a massive superior thin-walled filtering bleb in 1989 during treatment for *Haemophilus influenzae* and *Staphylococcus aureus* conjunctivitis. Initial treatment consisted of topical and intravenous antibiotics and topical steroids. Although the eye responded well to therapy a tiny Seidel-positive wound leak developed in the filtering bleb on the sixth day in hospital. The intraocular pressure by applanation tonometry was 3 mmHg, and the anterior chamber was shallow but not flat. Tissue adhesive was placed over the fistula site twice during the next three days. Because the patient could not tolerate pressure patching, topical antibiotic and steroid ointments were instilled every hour while she was awake. The day after the second application of tissue adhesive the filtering bleb was Seidel-negative. When the tissue adhesive was removed four days later, the conjunctiva had successfully healed over the wound leak. The conjunctival fistula has subsequently remained closed. While the patient was using no glaucoma eye drops, the intraocular pressure was 5 to 6 mmHg for the next two months and 9 to 10 mmHg for the subsequent three months.

CASE 5

A 73-year-old white female with angle closure glaucoma in the left eye controlled by a trabeculectomy performed in July 1989 developed a spontaneous, recurrent wound leak in a small, cystic filtering bleb. The original wound leak, which developed in October 1989, closed after application of a tissue adhesive and a bandage soft contact lens. Two weeks after the tissue adhesive was removed in April 1990 a recurrent fistula developed in the superonasal filtering bleb and did not close with several days of pressure patching. On examination a tiny Seidel-positive wound leak was noted in the portion of the filtering bleb overhanging the cornea. There was no infiltrate in or around the filtering bleb, and the anterior chamber was deep and quiet. The intraocular pressure by applanation tonometry was 12 mmHg while the patient was using timolol eye drops 0.5% twice daily. Tissue adhesive was applied to the wound leak site. The eye was treated with trimethoprim-polymyxin B (Polytrim) twice a day without pressure patching. The next day, the tissue adhesive was found dislodged into the inferior cul-de-sac, and the wound leak was still present. Tissue adhesive was reapplied, and the eye was pressure patched over a bandage soft contact lens. The next day

the tissue adhesive was in good position and a Seidel test was negative. One week later pressure patching was discontinued and frequent ointment instillation was started, dexamethasone-hypromellose (Maxidex) alternating with erythromycin every hour while the patient was awake. The bandage soft contact lens and the crystallised tissue adhesive were removed one month later. The fistula had closed and there was no evidence of a wound leak. However, a 1×1.5 mm corneal epithelial defect was present adjacent to the fistula site. This iatrogenic abrasion resolved in two days by continued frequent instillation of ointment. Since then, the intraocular pressure has been 13 to 14 mmHg while using only Timoptic.

Discussion

To our knowledge these five cases represent the largest reported series of leaking filtering blebs successfully closed with cyanoacrylate tissue adhesive. While it is an accepted treatment approach for this condition,^{14,15} only nine cases have been previously reported.¹⁻⁷ Other techniques for managing conjunctival fistulas in glaucoma filtering blebs have included conservative measures such as pressure patching, medications to decrease aqueous flow, bandage soft contact lens, scleral tamponade shell, collagen shield, and microsurgical suture repair or wound revision.⁸⁻¹⁵ All the surgical options require another invasive procedure with the operating room microscope and possibly retrobulbar or general anaesthesia. In contrast the application of tissue adhesive is easily performed under topical anaesthesia in the surgeon's consulting room without the aid of a microscope. In four of our five cases the tissue adhesive not only stopped the continuous external flow of aqueous humour, allowing the conjunctival defect to heal, but also preserved the integrity of the filtering bleb.

Conjunctival fistulas may develop either during glaucoma filtering surgery or as an early or late postoperative complication. During the operation leakage may result from a conjunctival buttonhole or tearing of the conjunctiva caused by suture tracks or instrument damage.⁸ In the early postoperative period leakage has traditionally been ascribed to inadequate closure of the conjunctival flap or failure to recognise buttonholes during surgery. Recently the use of 5-fluorouracil in high-risk glaucoma filtering surgery has introduced a new means by which these leaks may occur.¹⁶ In the late postoperative period a fistula may develop either spontaneously or from trauma and tends to occur in large, thin-walled blebs.⁹ Of the nine previously reported

Table 1 Clinical features of cases and results of treatment with tissue adhesive

Case	Date of filter surgery	Date of bleb leak	Aetiology of bleb leak	Number of times glue applied	IOP*		Post-treatment medication or surgery	Problems with tissue adhesive
					Pre	Post		
1	1971	1985	Spontaneous rupture	1	14	13	None	Corneal abrasion
2	1987	1988	Spontaneous rupture	2	4	8	Timolol	Corneal abrasion
3	1967	1988	Bacterial conjunctivitis	4	20	31	Repeat filter	None
4	1984	1989	Bacterial conjunctivitis	2	3	6	None	None
5	1989	1990	Spontaneous rupture	2	12	14	Timolol	Corneal abrasion

*Intraocular pressure.

cases treated by tissue adhesives six were of wound leaks occurring in the early postoperative period after glaucoma filtering procedures. In all five of our cases filtering bleb leaks developed as a remote complication following trabeculectomy, occurring anywhere from 10 months to 21 years postoperatively. Two of our patients developed filtering bleb leaks as a complication of bacterial conjunctivitis, while in the three other patients no antecedent cause could be identified.

On examining the clinical features and results of treatment in our five cases (Table 1) we can make several interesting observations. First, four eyes required more than one application of tissue adhesive. It may be necessary to vary the technique used after application to prevent the tissue adhesive from dislodging and to facilitate healing of the bleb leak. As adjuncts, pressure patching with or without bandage soft contact lenses and frequent ointment instillation were all successful in our series. One of the cases previously reported⁶ used tissue adhesive in conjunction with a collagen shield to close a conjunctival wound leak occurring after trabeculectomy. Secondly, three eyes had normal intraocular pressure in the presence of Seidel-positive bleb leak. The tendency was for eyes with multicystic blebs to have normal intraocular pressures, while those with thin, single walled blebs were hypotonous. Thirdly, four anterior chambers were deep in the presence of a Seidel-positive bleb leak. Apparently the breakdown of filtering blebs as a late complication does not immediately lead to hypotony or a flat chamber and may be overlooked on routine follow-up unless the eye is examined closely. Even when the intraocular pressure is normal and the chamber deep, filtering bleb leaks should be repaired to prevent endophthalmitis. Slow, low-flow leaks in old, well developed filtering blebs may be particularly suited for closure with tissue adhesive. Fourthly, three eyes developed corneal erosions at the site of tissue adhesive application adjacent to the leaking blebs. Corneal epithelial defects should be anticipated if the tissue adhesive extends on to the corneal surface.

Cyanoacrylate adhesives have been used in experimental and clinical ophthalmic surgery for almost 30 years.¹⁷ Tissue adhesives provide a valuable, non-surgical adjunct in the manage-

ment of wound leaks associated with penetrating keratoplasty, trauma, corneal thinning disorders, and descemetocoeles, as well as in glaucoma filtering surgery. The liquid adhesive n-butyl-2-cyanoacrylate forms a watertight seal with contacted tissues. This makes the material particularly suitable for certain ophthalmic procedures, including repair of corneal perforations and conjunctival fistulas. Although not a permanent seal, the adhesive maintains an environment that permits wound healing. We strongly recommend its use as a presurgical treatment in the management of leaking filtering blebs which occur as remote complications of glaucoma surgery.

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- 1 Grady FJ, Forbes M. Tissue adhesive for repair of conjunctival buttonhole in glaucoma surgery. *Am J Ophthalmol* 1969; 68: 656-8.
- 2 Awan KJ, Spaeth PG. Use of isobutyl-2-cyanoacrylate tissue adhesive in the repair of conjunctival fistula in filtering procedures for glaucoma. *Ann Ophthalmol* 1974; 6: 851-3.
- 3 Aminlari A, Sassani JW. Tissue adhesive for closure of wound leak in filtering operations. *Glaucoma* 1989; 11: 86-8.
- 4 Bechetolle A, Chabanais JL, Jallet G. Utilisation de la colle isobutyl-2-cyanoacrylate dans le traitement des fistules externes après trabeculectomie. *Bull Soc Ophthalmol Fr* 1977; 77: 765-7.
- 5 Ginsberg SP, Polack FM. Cyanoacrylate tissue adhesive in ocular disease. *Ophthalmic Surg* 1972; 3: 126-32.
- 6 Weber PA, Baker ND. The use of cyanoacrylate adhesive with a collagen shield in leaking filtering blebs. *Ophthalmic Surg* 1989; 20: 284-5.
- 7 Martinez LA, Miller KN, Brown RH, et al. The Nd: YAG laser removal of cyanoacrylate used to repair conjunctival wound leaks. *Am J Ophthalmol* 1989; 108: 86-7.
- 8 Petursson GJ, Fraunfelder FT. Repair of an inadvertent buttonhole or leaking filtering bleb. *Arch Ophthalmol* 1979; 97: 926-7.
- 9 Sugar HS. Complications, repair, and reoperation of anti-glaucoma filtering blebs. *Am J Ophthalmol* 1967; 63: 825-33.
- 10 Ruderman JM, Allen RC. Simmons' tamponade shell for leaking filtration blebs. *Arch Ophthalmol* 1985; 103: 1708-10.
- 11 Tomlinson CP, Belcher CD, Smith PD, et al. Management of leaking filtering blebs. *Ann Ophthalmol* 1987; 19: 405-8.
- 12 Epstein DL. *Chandler and Grant's glaucoma*. 3rd ed. Philadelphia: Lea and Febiger, 1986; 434-50.
- 13 Fourman S, Wiley L. Use of a collagen shield to treat a glaucoma filter bleb leak. *Am J Ophthalmol* 1989; 109: 673-4.
- 14 Hoskins HD, Kass MA. *Becker-Shaffer's diagnosis and therapy of the glaucomas*. 6th ed. St Louis: Mosby, 1989; 583-604.
- 15 Luntz MH, Harrison R, Schenker HI. *Glaucoma Surgery*. Baltimore: Williams and Wilkins, 1984; 124-44.
- 16 Rockwood EJ, Parrish RK, Heuer DK, et al. Glaucoma filtering surgery with 5-fluorouracil. *Ophthalmology* 1987; 94: 1071-8.
- 17 Refojo MF, Dohlman CH, Koliopoulos J. Adhesives in ophthalmology: a review. *Surv Ophthalmol* 1971; 15: 217-36.

MINI REVIEW

HTLV-I infection in human disease

Retroviral infection has been shown to cause neurological disease and leukaemia in man and there has recently been some interest, principally in Japan, on whether retrovirus infection might have ocular manifestations in its own right. The human T Lymphotropic virus (HTLV-I) is a member of the family Retroviridae, which has, as its name suggests, an affinity for T cells. Retroviruses are a single group of diploid RNA viruses, which encode synthesis of double-stranded DNA from a single strand of viral RNA (the usual flow of genetic information being in the opposite direction¹). The DNA, or provirus, subsequently becomes integrated into the host cell genome and serves as a template for viral replication.

There are four major classes of human retroviruses, but only two are linked causally with human disease: the oncoviruses, to which HTLV-I and the closely related HTLV-II belong, and the lentiviruses, which includes the human immunodeficiency viruses HIV-I and II. Although HTLV-I and HIV belong to different subgroups, they have a number of molecular, biological, and clinical features in common. These include a similar genomic arrangement and a tropism for CD4+ T lymphocytes, though the HTLV-I receptor has yet to be described. Both viruses are transmitted by the same routes, and infection can lead to neurological disorders, immunodeficiency, and cancer. HIV, however, unlike HTLV-I is not oncogenic in its own right and probably exerts its influence by derangement of immune surveillance. Although it was established that viruses now known as retroviruses were associated with animal tumours as long ago as 1908, when Rous described a sarcoma of chickens,² the first human retrovirus was not isolated until 1978. Robert Gallo and his coworkers isolated the virus from a cutaneous T cell lymphoma in a black American patient.³ This adult T cell leukaemia (ATL) is common among the people of the south-west islands of Japan.⁴ A second area of endemicity was found in 1982 in the Caribbean following the discovery of ATL in London patients all of whom were of Caribbean origin. HTLV-I is also endemic in parts of Africa.⁵ Further sporadic cases of ATL have been described in Caucasians in England and Italy and most recently from Brazil.⁶ Evidence from serological and molecular biological studies for the association of HTLV-I and ATL is convincing.⁷ In 1985 an association with tropical spastic paraparesis (TSP) was described in Martinique,⁸ and in Japan HTLV-I was shown to be associated with a second disease, known as HTLV-I associated myelopathy (HAM).⁹ TSP and HAM are now recognised as being the same disease and occur in the Caribbean, Africa, and South America as well as Japan and the Indian Ocean Islands and among migrants in the UK, USA, France, and Canada.

What then is the natural history of HTLV-I? How is it transmitted, and, once acquired, what are the risks for developing disease? Seroprevalence studies have shown that up to 20% of the inhabitants of south-west Japan and up to 10% of those of the Caribbean have antibodies to HTLV-I^{10,11} the seroprevalence showing a linear increase with age. The virus has been shown to be transmitted by three major routes; from mother to child,¹² through sexual intercourse,¹³ and by blood and blood products.¹⁴ The risk of perinatal infection is about 25%, transmission being mainly via breast milk and saliva with very little being transmitted in utero. The rate of

sexual transmission is about 6% per annum from male to female but only 1% from female to male, though this may increase in the presence of ulcerative genital disease. HTLV-I is highly cell associated and therefore, unlike HIV, can be transmitted only by whole blood or blood products but not by cell-free products such as plasma. It has been estimated that there is approximately a 60% chance of acquiring infection from a contaminated blood transfusion. It is interesting to note that both HTLV-I and HTLV-II are being found with increasing prevalence among intravenous drug abusers in Europe and the USA.¹⁵ The overall life time risk of ATL is 1-5% in persons affected before the age of 20.¹⁶ Both sexes are equally affected, which is probably a consequence of infection in childhood.

Tropical spastic paraparesis was first associated with HTLV-I in 1985 in Martinique, when 68% of patients with that condition were found to have antibodies to HTLV-I in their peripheral blood.¹⁷ This association has since been confirmed and expanded, and there appears to be no doubt that HTLV-I infection is the cause of this disease. The prevalence of TSP is about 12-28/100 000 of total population in endemic areas, which is partly due to the length of survival of patients with TSP. Women are three times more likely to develop the disease than men, which reflects the greater seroprevalence in adult women, infection being acquired either in childhood or in adult life.

The clinical picture of TSP is of a chronic progressive paraparesis without remissions starting in adulthood which predominantly affects the pyramidal tracts with sphincter involvement. Back and radicular pain are common, and the upper limbs are relatively spared. The disease has some similarity with certain forms of multiple sclerosis (MS), which has led to considerable interest in the role of retrovirus infection in the pathogenesis of MS. However, TSP in its recognised form is clinically, pathologically, and virologically different. Antibodies to HTLV-I are found in the serum and cerebrospinal fluid. The virus has been identified in neurological tissue, and the pathology is of an adhesive arachnoiditis and vasculitis.¹⁸ Magnetic resonance imaging scans can show similar white matter lesions in the cerebrum, pons, and cerebellum to those of MS, but, in contrast to MS, involvement of the visual system is usually subclinical. A French study¹⁹ of 167 patients with chronic idiopathic myelopathies identified 10 cases with HTLV-I infection. In this study eight of these patients were from endemic areas, but two had never lived outside France. Although there was subclinical optic nerve involvement in four out of the nine patients tested, no patient appears to have been symptomatic. A link between TSP and West Indian amblyopia²⁰ has been suggested, but it remains to be established whether dietary factors are more likely to be contributory.

Although HTLV-I is associated with ATL and TSP, most patients with HTLV-I infections remain asymptomatic throughout their life. Whether a patient develops ATL or TSP may depend on genetic susceptibility,^{21,22} and it is rare for both conditions to exist in the same patient. HTLV-I infection has also been associated with polymyositis in Jamaica²³ and Sjögren's syndrome²⁴ as well as a variety of visual disorders in south-west Japan which, apart from opportunistic retinopathies in patients with ATL, include

idiopathic cotton-wool spots, pigmentary retinopathy, and granulomatous uveitis.²⁵ Five of 34 consecutive patients with TSP had a granulomatous anterior uveitis,²⁶ and in another series four of 38 patients with TSP had an idiopathic pigmentary retinopathy.²⁷

A paper in last month's issue of the *BJO* from the same authors explores this further and suggests that HTLV-I is associated with idiopathic granulomatous anterior uveitis in a considerable number of their patients with this condition (41% or 18 of 44 patients; two of these had recurrent episodes). Although these patients were HTLV-I positive, they had no other signs of neurological or haematological disease. Potential analogies could be drawn both to multiple sclerosis, in which some patients have a very similar type of uveitis, and to the high incidence of ocular pathology in patients with HIV infection, though this is of a rather different nature. It remains to be established in these patients whether uveitis is predictive of the development of neurological or haematological disease. Also undetermined is whether HTLV-I represents a truly causative agent of uveitis in these patients and, if so, whether it is a disease of significance only in areas of high endemic infection, or whether HTLV-I or other retrovirus infections are an important factor in ocular disease elsewhere.

The prevalence of HTLV-I seropositivity in Britain is unknown, but a local study in Lambeth showed that there was an incidence of 0.37% in patients screened routinely for antenatal assessment. Half of these were of West Indian origin, a quarter West African, and the remainder unknown. This low incidence in the indigenous UK population may suggest that HTLV-I infection is itself unlikely to be an important association of granulomatous anterior uveitis here.

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- 1 Baltimore D. RNA dependent polymerase in virions of RNA tumour viruses. *Nature* 1970; 226: 1209-11.
- 2 Rous P. Sarcoma of the fowl transmissible by an agent separable from the tumor cells. *J Exp Med* 1911; 13: 397.
- 3 Kalyanaraman VS, Sarngadharan MG, Poiesz B, Ruscetti FW, Gallo RC. Immunological properties of a type C retrovirus isolated from cultured

- human T lymphoma cells and comparison to other mammalian retroviruses. *J Virol* 1981; 38: 906-15.
- 4 Hinuma Y, Komoda H, Chosa T, et al. Antibody to adult T-cell leukaemia virus associated antigen (ATLA) in sera from patients with ATL and controls in Japan. *Int J Cancer* 1982; 29: 631-5.
- 5 Pombo de Oliveira MS, Matutes E, Famadas L, et al. Adult T-cell leukaemia lymphoma in Brazil and its relation to HTLV-I. *Lancet* 1990; 336: 987-90.
- 6 Huntmann G, Schneider J. Antibodies to ATL/HTLV-I in Africa. *Med Microbiol Immunol* 1984; 173: 167-70.
- 7 Hinuma Y, Nagata K, Hanaoka M, et al. Adult T cell leukaemia virus-associated antigen (ATLA) in an ATL cell line and detection of antibodies to the antigen in human sera. *Proc Natl Acad Sci USA* 1981; 78: 7864-76.
- 8 Gessain A, Barin F, Vernin JC, et al. Antibodies to HTLV-I in patients with TSP. *Lancet* 1985; ii: 1031-2.
- 9 Osame M, Usuku K, Izumo S, et al. HTLV-I-associated myelopathy, a new clinical entity. *Lancet* 1986; ii: 1031-2.
- 10 Levine PH, Blattner W, Clark J, et al. Geographic distribution of HTLV-I and identification of a new high-risk population. *Int J Cancer* 1987; 40: 741-6.
- 11 Tajima K, Kamura S, Ito S, et al. Epidemiological features of HTLV-I carriers and incidence of ATL in an ATL endemic island. *Int J Cancer* 1987; 40: 741-6.
- 12 Komuru A, Hayami M, Fujii H, et al. Vertical transmission of ATL virus. *Lancet* 1983; i: 240.
- 13 Nakano S, Ando Y, Ichijo M, et al. Search for possible routes of vertical and horizontal transmission of adult T cell leukaemia virus. *Gann* 1984; 75: 1044-5.
- 14 Okochi K, Sato H, Hinuma Y. A retrospective study on transmission of adult T cell leukaemia virus by blood transfusion; seroconversion of recipients. *Vox Sang* 1984; 46: 245-53.
- 15 Robert-Eurot M, Weiss JH, Giron JA, et al. Prevalence of antibodies to HTLV-I, II, III in IVDA from an AIDS endemic region. *JAMA* 1986; 225: 3133-7.
- 16 Kondo T, Kono H, Nonaka H, et al. Risk of adult, T cell leuk/lymphoma in HTLV-I-carriers. *Lancet* 1987; ii: 159.
- 17 Gessain A, Barin F, Vernin JC, et al. Antibodies to human T lymphotropic virus type I in patients with tropical spastic paraparesis. *Lancet* 1985; 2: 407-410.
- 18 Roman GC, Schoenberg BS, Spencer PS, et al. Tropical spastic paraparesis in the Seychelles Islands of the Indian Ocean. Clinical neurophysiological and pathological features. *Neurology*, 1986; 36 (suppl J): 106.
- 19 Gant O, Gessain A, Bolger F, et al. Chronic myelopathies associated with human T lymphotropic virus type I. A clinical, serological and immunovirologic study of 10 patients in France. *Arch Neurol* 1989; 46: 255-60.
- 20 Montgomery RD, Cruikshank EK. Clinical and pathological observation on Jamaican neuropathy: a report on 206 cases. *Brain* 1964; 87: 425-62.
- 21 P Rudge. Tropical spastic paraparesis and human T cell lymphotropic virus. (Editorial.) *J Neurol Neurosurg Psychiatry* 1990; 53: 2-3.
- 22 Kayembe K, Goubau P, Desmyter J, et al. A cluster of HTLV-I associated tropical spastic paraparesis in Equateur (Zaire): ethnic and familial distribution. *J Neurol Neurosurg Psychiatry* 1990; 53: 4-10.
- 23 Morgan O, Rodgers-Johnson P, Mora C, Char G. HTLV-I and polymyositis. *Lancet* 1989; ii: 1184-7.
- 24 Vernant JC, Buissen G, Madgeleine J, et al. T lymphocytic alveolitis, tropical spastic paraparesis and Sjogren's syndrome. *Lancet* 1989; i: 177.
- 25 Ohba N, Matsumoto M, Sameshima M, et al. Ocular manifestations in patients infected with human T-lymphotropic virus type I (HTLV-I). *Jpn J Ophthalmol* 1989; 33: 1-12.
- 26 Nakao K, Ohba N, Matsumoto M. Non-infectious anterior uveitis in patients infected with T-lymphotropic virus types I. *Jpn J Ophthalmol* 1989; 33: 472-81.
- 27 Nakao K, Ohba N, Isashiki M, et al. Pigmentary retinal degeneration in patients with HTLV-I-associated myelopathy. *Jpn J Ophthalmol* 1989; 33: 383-91.

CASE REPORTS

Hyperkalaemia induced by carbonic anhydrase inhibitor

Yasuhisa Wakabayashi

Abstract

An 81-year-old man developed hyperkalaemic and hyperchloraemic metabolic acidosis following treatment with a carbonic anhydrase inhibitor for his glaucoma. He had mild renal failure and selective aldosterone deficiency was confirmed. In this case the treatment did not lead to hypokalaemia because of the limited potassium secretory capacity in the renal tubules from selective aldosterone deficiency; rather, it may have led to hyperkalaemia because metabolic acidosis induced by the carbonic anhydrase inhibitor caused transcellular movement of potassium.

Carbonic anhydrase inhibitors (CAIs) are widely used in the treatment of glaucoma. Hypokalaemic and hyperchloraemic metabolic acidosis is one of the common adverse effects, particularly observed in elderly patients with mild renal impairment or diabetes mellitus.¹ This is a report on a patient who developed hyperkalaemic metabolic acidosis following treatment with a CAI.

Case report

An 81-year-old man presented with developing blurred vision. Glaucoma and cataract were diagnosed, and he was first treated with topical timolol maleate. The ocular pressure was poorly controlled and he was admitted for an operation. A carbonic anhydrase inhibitor, dichlorphenamide, was given in the dosage of 25 mg a day prior to operation. Five to seven days after starting treatment confusion and disorientation were noted, associated with hyperkalaemic and hyperchloraemic metabolic acidosis. Dichlorphenamide was discontinued and he was referred to the renal division. Timolol maleate was not discontinued.

He was known to have mild renal dysfunction, but diabetes mellitus was not noted. On examination he was fully conscious and well orientated. He was mildly dehydrated but otherwise appeared normal. The laboratory findings are summarised in Table 1. The hyperkalaemic metabolic acidosis was corrected after treatment with sodium bicarbonate. He then moved to the ophthalmic division to undergo right intracapsular cataract extraction and peripheral iridectomy. Dichlorphenamide was given again in the dosage of 100 mg a day on the day of operation. Polyuria, disorientation, and hyper-

Table 1 Laboratory findings

Urine pH		5.5
Arterial pH		7.23
PaCO ₂	kPa	4.0
Total protein	g/l	78
Urea nitrogen	mmol/l	16.3
Creatinine	μmol/l	183
Sodium	mmol/l	133
Potassium	mmol/l	6.4*
Chloride	mmol/l	110
Bicarbonate	mmol/l	12
Anion gap	mmol/l	11
Phosphorus	mmol/l	3.3
Glucose	mmol/l	4.8

*The serum potassium concentration was 5.0 mmol/l on admission.

kalaemia developed again after the operation. The CAI was discontinued. The symptoms soon subsided and the serum potassium concentration returned to normal without a use of sodium bicarbonate (Fig 1). He underwent an operation on the contralateral side without pretreatment with a CAI. The postoperative course was uneventful. To investigate the cause of hyperkalaemic and hyperchloraemic metabolic acidosis, the renal response to acid, alkali, and furosemide load was examined while he was off all medications (Table 2).

Discussion

Hypokalaemic and hyperchloraemic metabolic acidosis has been commonly observed after treatment with CAIs.^{2,3} The CAI administration results in an increase in renal tubular flow, which is thought to enhance potassium excretion, and profound loss of potassium in the urine causes hypokalaemia.⁴ In the case reported here, hyperkalaemia rather than hypokalaemic metabolic acidosis developed. The results of NH₄Cl,

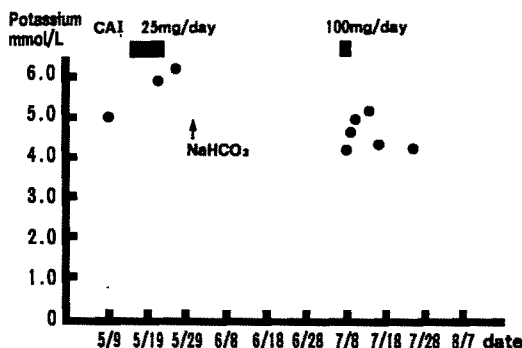


Figure 1 Serum potassium concentration rose following administration of the CAI and fell after the CAI was discontinued.

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Table 2 Renal response to acid, alkali, and furosemide load

	<i>NH₄Cl</i> provocative test	<i>NaHCO₃</i> loading test	<i>Furosemide</i> loading test
Plasma HCO_3^- mmol/l	16	25	
Urine pH	4.8		
PaCO_2 kPa	4.0		
FEHCO_3^- %		<10	
U-B PCO_2 kPa		3.3	
PAC pmol/l			89*

FEHCO_3^- : fractional excretion of bicarbonate.

U-B CO_2 : difference of partial pressure of carbon dioxide between urine and blood.

PAC: plasma aldosterone concentration.

*Furosemide was given in the dose of 1 mg/kg body weight intravenously.

PAC was 119 pmol/l before furosemide loading.

NaHCO_3 , and furosemide loading tests indicated that selective aldosterone deficiency was complicated by mild renal failure.³ Thus potassium secretory capacity was thought to be limited, and the CAI did not cause renal loss of potassium in this case. Instead metabolic acidosis from bicarbonate loss by the CAI might have caused transcellular movement of potassium, yielding extracellular hyperkalaemia.

The topical use of timolol maleate might have also contributed to the development of hyper-

kalaemia by suppressing renin (and aldosterone) secretion.⁶ But hyperkalaemia was considered to be induced chiefly by the CAI, since timolol maleate was given throughout the entire clinical course and hyperkalaemia was not observed unless the CAI was given (Fig 1).

This is apparently the first report of hyperkalaemic metabolic acidosis induced by a CAI. CAIs could cause hyperkalaemia when given to patients who have a limited capacity for secreting potassium in the renal tubules, as seen in patients with renal dysfunction of tubular origin or to whom a β adrenergic antagonist is given concomitantly.

- 1 Maisiey DN, Brown RD. Acetazolamide and symptomatic metabolic acidosis in mild renal failure. *Br Med J* 1981; 283: 1527-8.
- 2 Epstein DL, Grant WM. Carbonic anhydrase inhibitor side effects - serum chemical analysis. *Arch Ophthalmol* 1977; 95: 1378-82.
- 3 Heller I, Halvey J, Cohen S, Theodor E. Significant metabolic acidosis induced by acetazolamide - not a rare complication. *Arch Intern Med* 1985; 145: 1815-7.
- 4 Sebastian A, McSherry E, Morris RC Jr. Renal potassium wasting in renal tubular acidosis (RTA). *J Clin Invest* 1971; 50: 667-78.
- 5 Sebastian A, Schambelan M, Lindenfeld S, Morris RC Jr. Amelioration of metabolic acidosis with fludrocortisone therapy in hyporeninemic hypoaldosteronism. *N Engl J Med* 1977; 297: 576-83.
- 6 Swenson ER. Severe hyperkalemia as a complication of timolol, a topically applied β -adrenergic antagonist. *Arch Intern Med* 1986; 146: 1220-1.

Endophthalmitis after removal of an encircling band

C E Hugkulstone, A S Rubasingham

Abstract

A case of endophthalmitis following the removal of an encircling band is presented. A possible route of entry in the absence of scleral perforation during the procedure is proposed.

After retinal detachment surgery, scleral buckles may need to be removed because of infection, erosion, extrusion, pain,¹⁻⁴ or to reduce post-operative diplopia.⁵ The major complication associated with their removal is the risk of redetachment, with rates varying between 4%³ and 33%.¹

We report a case of endophthalmitis following the removal of a scleral band.

Case report

A 36-year-old man was first seen in June 1988 with a subtotal retinal detachment in the left eye. He underwent an encircling procedure with a 2 mm silicone band secured at the equator with 5/0 Dacron sutures, with the sleeve in the superotemporal quadrant. Subretinal fluid was drained in the superotemporal quadrant as well. Postoperatively he was treated with Betnesol-N drops (betamethasone and neomycin) for six weeks.

Following surgery he complained of continuous pain in that eye, and he was admitted to hospital in March 1990 for release of the strap. He received no preoperative antibiotics.

Under general anaesthesia the conjunctiva was incised in three positions close to the strap site, and the fibrous capsule was dissected with blunt spring scissors. The strap was then divided and removed by gentle traction alone. The conjunctiva was closed with 6/0 catgut, and chloramphenicol ointment was instilled. The following day the eye was settling satisfactorily and he was discharged home on twice daily chloramphenicol ointment.

Two days later he was readmitted with severe pain in the left eye and loss of vision. The visual acuity was perception of light. There was slight corneal epithelial oedema, a 2 mm hypopyon, and no red reflex could be elicited.

A pars plana vitreous tap was performed under local anaesthesia. Direct microscopy revealed a few leucocytes and Gram-positive cocci, and culture of the specimen grew *Staphylococcus epidermidis*.

He was treated with intracameral, subconjunctival, topical and systemic gentamicin, and systemic prednisolone was started after 48 hours. The endophthalmitis responded to treatment, and by seven weeks he had regained his pre-

operative visual acuity of 6/36. The retina has remained attached after four months' follow-up.

Discussion

At first sight this would appear to be a straightforward case of exogenous endophthalmitis. The classical organism was isolated⁶ and the onset was within 48 to 72 hours following surgery. However, the difficulty lies in the route of entry of the organism. There was no evidence of perforation of the globe during surgery, and no sutures were removed. No endogenous source for this infection was found.

It is possible that the site of the previous subretinal fluid drainage was disturbed by surgery, permitting direct entry of this normally commensal organism into the globe. This may have been aggravated by the scleral thinning that can occur beneath an encircling band,⁴ though there was no evidence of obvious scleral erosion in our patient.

Previous reports of the removal of scleral buckling elements have naturally concentrated on the risks of redetachment.¹⁻⁴ However, one paper³ does record a single case with intraocular exudate noted over the surface of the buckle, which resolved on removal of the buckle and administration of systemic antibiotics and steroids (though no vitreous tap was performed). There is also a solitary case from another series⁴ in which phthisis occurred from 'unexplained chronic intraocular inflammation' following removal of a scleral buckle. But there is no mention of proved postoperative endophthalmitis as a possible complication, despite some of these explants being removed because of infection.¹⁻⁴ This may be because the majority of infected buckles are removed somewhat sooner than in our case,¹⁻³ so reducing the extent of scleral thinning.

Although a single case report provides only weak grounds for any recommendations, the use of subconjunctival antibiotics may be prudent after the removal of scleral buckles, especially if previous drainage of subretinal fluid has been performed.

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- 1 Ulrich RA, Burton TC. Infections following scleral buckling procedures. *Arch Ophthalmol* 1974; 92: 213-5.
- 2 Schwartz PL, Pruett RC. Factors influencing retinal redetachment after removal of buckling elements. *Arch Ophthalmol* 1977; 95: 804-7.
- 3 Hilton GF, Wallyn RH. The removal of scleral buckles. *Arch Ophthalmol* 1978; 96: 2061-3.
- 4 Lindsey PS, Pierce LH, Welch RB. Removal of scleral buckling elements. Causes and complications. *Arch Ophthalmol* 1983; 101: 570-3.
- 5 Fison PN, Chignell AH. Diplopia after retinal detachment surgery. *Br J Ophthalmol* 1987; 71: 521-5.
- 6 Diamond JG. Intraocular management of endophthalmitis. A systematic approach. *Arch Ophthalmol* 1981; 99: 96-9.

Bilateral Norrie's disease in identical twins

K Sukumaran

Abstract

A case of Norrie's disease in an identical twins is reported. No positive family history was obtained. The couple had no other children. The older of the twins died at the age of 9 months of uncertain cause. To the best of my knowledge this is the first case of Norrie's disease reported in Malaysia. And its occurrence in an identical twins is very rare.

A pair of male identical Chinese twins, A and B aged 3 months, were brought by their parents to the Eye Clinic of the University Hospital, Kuala Lumpur, Malaysia, with a complaint of bilateral white pupil.

On examination, twin A, the older, had a left cloudy cornea of one week's duration. The birth weight was 1360 g and the child was born prematurely at the seventh month of an uncomplicated pregnancy by a spontaneous vaginal delivery in a private hospital near by. Oxygen was given for 20 days. Hepatosplenomegaly was present; the liver was enlarged 4 cm and the spleen 1 cm.

The child was examined under general anaesthesia. There was central stromal opacity of the left cornea, and the left fundal view was hazy. However, there was a diffuse white growth on both the retinae. There were areas of adhesions between the iris and the anterior capsule of the lens in the left eye. Neovascularisation of the iris was also present. The anterior chamber was shallow. Similar findings were seen in his right eye. The horizontal and vertical corneal diameters in both eyes were within normal limits. The intraocular pressures of the left and right eyes were 21.9 and 21.3 mmHg respectively by Schiötz tonometer. A clinical diagnosis of bilateral retinoblastoma was made, and his left eye was enucleated. Histopathological examination did not reveal a tumour but retinal dysplasia.

Twin B, the younger, had haziness of both corneas of one week's duration. The birth weight was also 1360 g, and the baby was born about 16 minutes after the first twin. This child also received oxygen for the first 20 days of life.

The child was examined under general anaesthesia. Both the fundi, though poorly visible owing to corneal haziness, showed whitish growths in the retinae with poor details. Rubeosis iridis was present in both eyes, and the anterior chambers in both eyes were shallow. The horizontal and vertical diameters in both eyes were within normal limits. The intraocular pressures of right and left eyes were 21.9 and 10.9 mmHg respectively by Schiötz tonometer. A clinical diagnosis of bilateral retinoblastoma was made, and his right eye was enucleated. Histopathological examination revealed retinal dysplasia of the right eye.

The anthropometric chart was similar in both

infants. The head circumference was 50th percentile, length was less than 3rd percentile, and the weight less than 10th percentile. The percentiles on this anthropometric chart were based on data from H C Stuart and associates, Harvard School of Public Health, Boston.

The first twin was not so active as the second. In view of the bilateral eye involvement of both infants, specimens were sent to the Institute of Ophthalmology, London, for an expert opinion from Professor A Garner. His report was as follows.

Twin A. 'The retina was completely detached and whilst there was much distortion due to folding, I think there may also be some true dysplastic rosette formation. The subretinal space is filled with serohaemorrhagic exudate and there is some hyperplasia of the ciliary processes. The surface of the detached retina is covered in part by a layer of vascularised fibrous tissue which is, in turn, adherent to the posterior capsule of the lens. One leaf of the iris is pressed against the back of the cornea, which is slightly oedematous.'

Twin B. 'The only difference is an absence of iris displacement. These histological findings occurring in male infants are strongly suggestive of the X-linked Norrie's disease in which corneal opacities, elongated ciliary processes, retinal detachment and dysplasia with haemorrhagic sub-retinal exudate are all described.'

Discussion

Atrophia oculi congenita was a type of congenital blindness first described by the Danish ophthalmologist, G Norrie,¹ in 1927 after having surveyed the causes of blindness in Denmark. The term 'Norrie's disease' was actually proposed by Warburg for congenital bilateral pseudotumour of retina with recessive X-linked chromosomal transmission.² The gene is carried by females and the disease affects only males.³

The exact pathogenesis of Norrie's disease is not clear. Warburg believed that a genetically determined biochemical defect induces an early arrest in retinal development, with associated malformation of the primary and secondary vitreous.⁴ Neuroectodermal changes also occur in the cerebral cortex and auditory nerve.⁴ Clinical and histopathological similarities between Norrie's and Coats's disease have been suggested.⁵

Norrie's disease, which is rare,⁶ has been reported in other parts of the world.⁷ To the best of my knowledge this is the first case reported in Malaysia, and possibly its occurrence in identical twins is very rare.

Though varying degrees of hearing impairment and mental retardation have been described, this pair of twins clinically revealed no such abnormality at the time of examination.

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There was no family history of blindness, and this was the mother's first pregnancy. Since this disease is not common, a strong diagnosis of retinoblastoma was considered and hence the enucleation. CT scan was not available in the hospital then. The problem of differentiating a pseudoglioma from retinoblastoma may be difficult in infants and children, and a thorough knowledge of the family history is of great value. Unfortunately, the parents of this pair of twins failed to keep follow-up appointments, but we know from them that the elder of the twins died at 9 months of age of undetermined cause. Permission to photograph the twins before and

after enucleation was refused.

- 1 Norrie G. Causes of blindness in children. Twenty five years experience of Danish institutes for the blind. *Acta Ophthalmol (Kbh)* 1927; 5: 357-86.
- 2 Warburg M. Norrie's disease: a new hereditary bilateral pseudotumour of the retina. *Acta Ophthalmol (Kbh)* 1961; 39: 757-72.
- 3 Taylor PJ, Coates T, Newhouse ML. Episkopi blindness: hereditary blindness in a Greek Cypriot family. *Br J Ophthalmol* 1959; 43: 340-4.
- 4 Warburg M. Norrie's disease and falciform detachment of the retina. In: Goldberg M, ed. *Genetic and metabolic aspects of eye disease*. Boston: Little, Brown, 1974: 441-6.
- 5 Blodi F, Hunter, W. Norrie's disease in North America. *Doc Ophthalmol* 1969; 26: 434-50.
- 6 Norrie's disease: a congenital progressive oculo-acoustico-cerebral degeneration. *Acta Ophthalmol (Kbh)* 1966; 89 (suppl): 1-47.
- 7 Axel C. Norrie's disease. *Am J Ophthalmol* 1968; 66: 328-32.

Pathological changes in levator palpebrae superioris muscle treated with botulinum toxin in a case of carotico-cavernous fistula

G G W Adams, P N Dilly

Abstract

We describe the case of a patient with carotico-cavernous fistula who had botulinum toxin A to induce a protective ptosis 4-5 days before death. The levator palpebrae superioris muscle from both sides and the superior rectus muscle from the injected side were obtained for examination. The preserved samples were stained with haematoxylin and eosin, Martius scarlet blue, Glees, S100, dehydrogenase, ATPase, and toluidine blue as well as being examined by electron microscopy. Inflammation and oedema were found that were probably due to the carotico-cavernous fistula. Axonal and some myelin sheath damage were also seen.

Botulinum toxin A (BTXA), has been used clinically since 1979 in the USA and since 1982 in Britain. It was initially for the treatment of strabismus, but later uses have included the treatment of blepharospasm and hemifacial spasm. More recently it has been used to produce a ptosis as an alternative to tarsorrhaphy. The toxin is bound to nerve terminals that release acetylcholine, where it prevents the release of the transmitter and produces a flaccid paralysis of muscle.

Although work has been published on the effects of botulinum poisoning on animal muscle, we are unaware of any published data on the effects on the human extraocular muscles.

Materials and methods

The material obtained at necropsy came from a 45-year-old Caucasian female who had been diagnosed as having a carotico-cavernous fistula in early 1988 but who refused further investigations or treatment at that time. In September 1988 she returned with gross proptosis of the right eye and reduced vision. She had noticed that the noise in her head was reduced. During her admission for investigations she was started on high-dose systemic steroids, 60 mg prednisolone each day, to reduce orbital swelling and proptosis. The proptosis was reduced, but she developed exposure keratitis with hypopyon ulcer. Intensive treatment with topical antibiotics produced some improvement, but in view of her continuing proptosis and the consequent corneal exposure a central tarsorrhaphy under local anaesthetic was performed. On the following day an injection of 62.5 µg BTXA in 0.1 normal saline was given in the region of the right levator palpebrae superioris (LPS) muscle to produce a flaccid paralysis of the muscle to help prevent the

tarsorrhaphy pulling apart. The next four and a half days were complicated by an acute duodenal ulcer that required surgical repair. She succumbed to an acute myocardial infarction.

Permission to remove the levator muscle from both orbits was given by the coroner. At necropsy the levator palpebrae superioris muscle was taken from both sides and the superior rectus muscle on the treated side was also removed for examination.

The specimens were divided longitudinally and transversely, and pieces were preserved in glutaraldehyde, formol saline, and by freezing. Specimens from each muscle were stained with haematoxylin and eosin, Martius scarlet blue, Glees, S100, dehydrogenase, ATPase at varying pHs, and toluidine blue techniques, as well as examined with the electron microscope.

Results

Haematoxylin and eosin staining for the general morphology of the specimens demonstrates the LPS from the injected side to have inflammation and oedema (Fig 1). The muscle fibres, which were of uneven width, were widely separated from each other by pale irregular spaces indicative of oedema. These changes were not found in the control muscle, in which there was no 'bubbly' oedema; here the fibres were tightly packed and of regular width (Fig 2). The blood vessels on the injected side were very abnormal and appeared thrombosed, with hyaline-like fibrin clot and no identifiable red blood cells in many of the vessels. There was also perivascular cuffing, particularly with lymphocytes, but some plasma cells could also be seen (Fig 3). The congestion of the blood vessels and their thrombosis can best be explained as the result of the carotico-cavernous fistula, which at necropsy was found to be completely thrombosed. The vessels on the normal side did not show any inflammation, and there were generally RBCs rather than clot in them. They were perhaps slightly distended, an effect of back pressure from the fistula.

The superior rectus muscle from the injected side also showed similar changes to those found in its companion LPS (Fig 4).

Martius scarlet blue is a trichrome stain for connective tissue and muscle. In the sections from the injected side the muscle cell nuclei were centrally placed in contrast to those in sections of the control muscle, where they were found in their usual position in the periphery (Figs 5, 6). This change is usually associated with regeneration of necrotic muscle. The muscle striations were much more broken up in the treated than in the untreated muscle. There was also patchy

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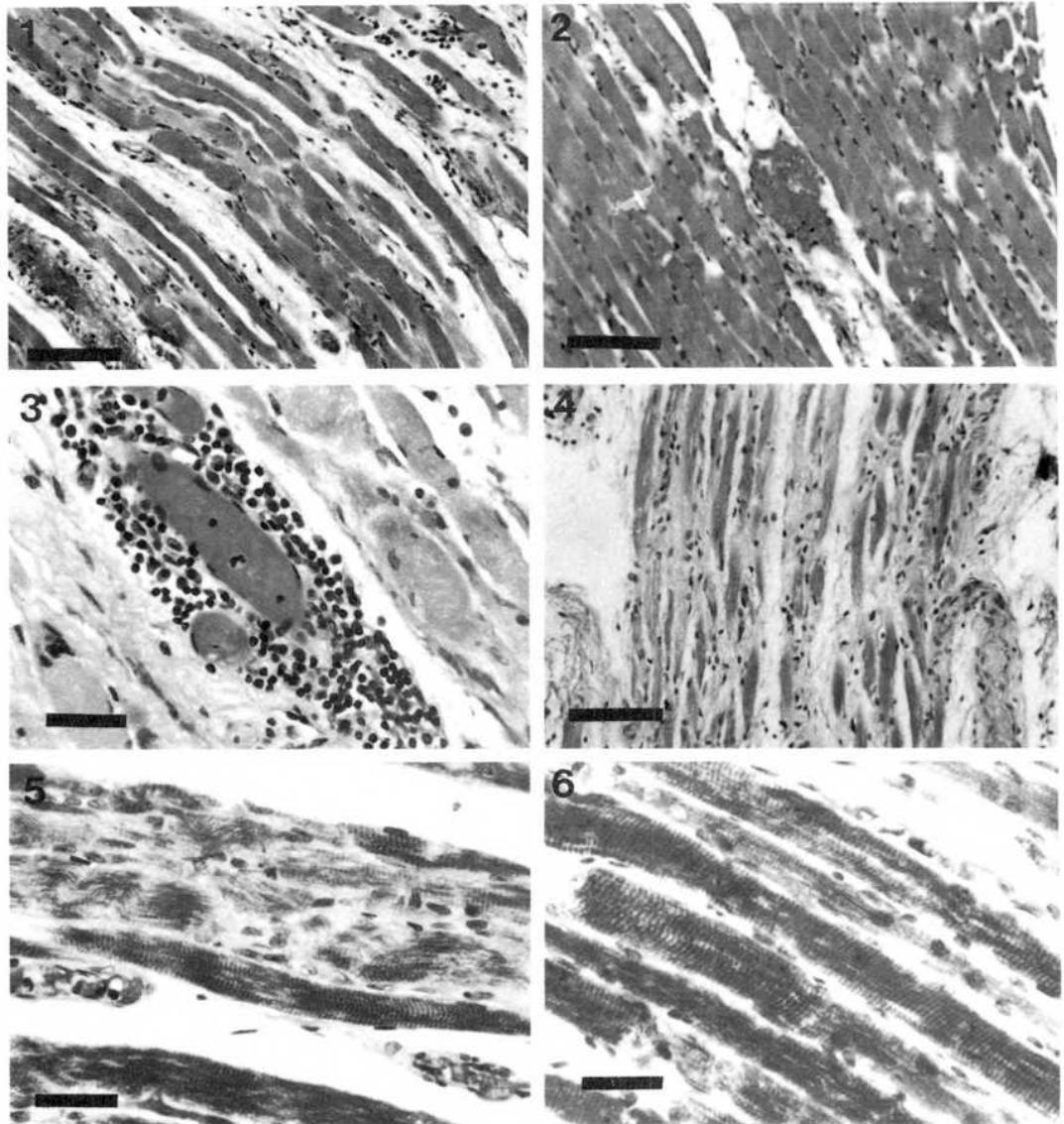


Figure 1 BTXA treated levator to show uneven muscle fibres separated by oedema. (H-E, bar=100 μ m.)

Figure 2 Normal levator muscle to show tightly packed muscle fibres of even width. Blood vessel a little distended, but with no inflammatory cuffing. (H-E, bar=100 μ m.)

Figure 3 BTXA levator muscles to show thrombosed blood vessel full of fibrin clot, with perivascular cuffing. (H-E, bar=25 μ m.)

Figure 4 Superior rectus from botulinum treated side, showing similar changes of uneven muscle fibres separated by oedema. (H-E, bar=100 μ m.)

Figure 5 BTXA levator muscle, to show central nucleolation of muscle fibres. (Martius scarlet blue, bar=25 μ m.)

Figure 6 Normal levator muscle, to show normal muscle fibres with peripherally placed nuclei. (Martius scarlet blue, bar=25 μ m.)

staining of muscle fibres, with disrupted organisation of sarcomeres. This is most likely to be a hypoxic change secondary to the fistula.

The Glee's technique stains nerve fibre axons, but not their myelin sheaths. There appeared to be considerable damage to the nerves of the LPS on the injected side, as shown by the break up of the silver of the axons in comparison with the staining on the non-injected side (Figs 7, 8). There was much damage and very few if any staining intact axons. This finding of nerve fibre damage in BTXA treated muscle has not been reported from animal experiments.

S100 stains Schwann cells and so displays myelin rather than axons. Some sections of the nerves from the botulinum treated levator showed little content (Fig 10). The myelin sheaths appeared either granular or empty in comparison with the normal side (Fig 10). The changes in the Schwann cells were not marked

and were more patchy in distribution than the nerve fibre change.

Dehydrogenase reductase is an indicator of mitochondrial distribution and activity. As type 1 muscle has larger numbers of mitochondria than other types of muscle, it can help to differentiate different muscle fibre types. This stain was thought to show a normal appearance in both the treated (Fig 11) and the control muscle (Fig 12).

The ATPase reaction with preincubation at different pHs disrupts the normal myofibrillary network of the muscle and allows estimation of the fibre types 2A, 2B, and 2C, while the type 1 fibres stain weakly with this method. There was some change in the sample preincubated at pH 4.3 but no difference in the others. This finding is consistent with a hypoxic effect (Figs 13, 14).

Toluidine blue was used as the stain to prepare tissue prior to electron microscopy. Some sections showed a snake-like pattern of fibril bundles

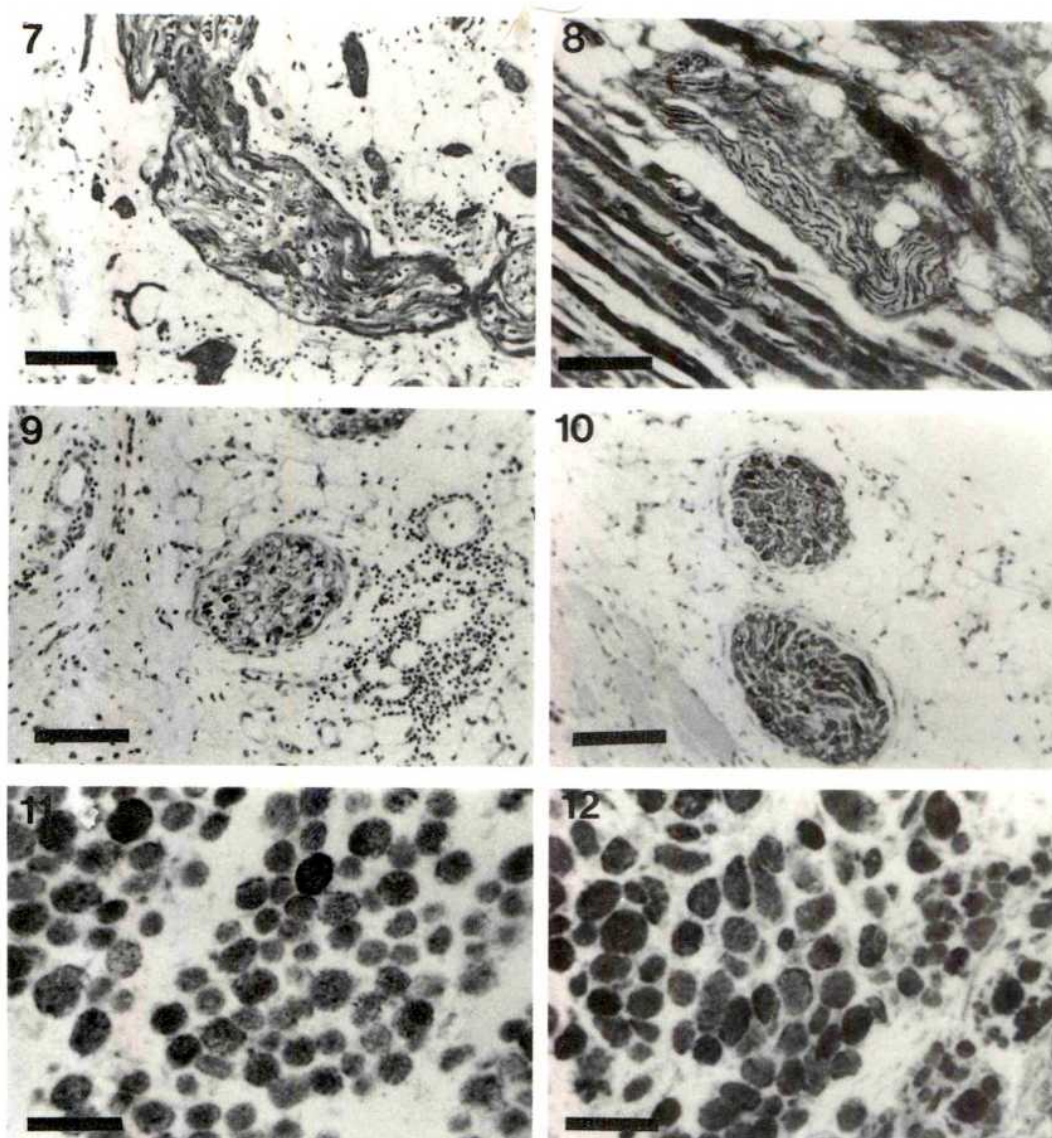


Figure 7 BTXA levator muscle, to show broken up axonal staining. (Glee stain, bar=100 μ m.)
 Figure 8 Normal levator muscle, to show normal axonal staining. (Glee stain, bar=100 μ m.)
 Figure 9 BTXA levator muscle, to show reduced Schwann cell staining. (S100 stain, bar=100 μ m.)
 Figure 10 Normal levator muscle, to show normal myelin staining of Schwann cells. (S100 stain, bar=100 μ m.)
 Figure 11 BTXA levator muscle. (Dehydrogenase, bar=100 μ m.)
 Figure 12 Normal levator muscle. (Dehydrogenase, bar=100 μ m.)

on the injected side, with muscle fibres coming away from the sarcolemma (Figs 15, 16).

Electron microscopy shows PM change in the mitochondria. There was blurring of the Z lines in muscle on the BTXA side which may equate with the 'streaming' of Z lines in mouse work (Figs 17, 18).¹

Discussion

A carotico-cavernous fistula leads to reduced arterial pressure in the ophthalmic artery and increased pressure in the orbital veins. This reduces the A-V pressure gradient, causing tissue hypoxia from the lowered ocular pressure.² Previous pathological examination of extraocular muscle from cases of carotico-cavernous fistula has shown infiltration with chronic inflammatory cells but no evidence of ischaemic necrosis.¹ 4-5 days is sufficient time for BTXA to produce a protective ptosis. Obviously with a central tarsorrhaphy in situ this could not be proved, but the lids did appear to be laxer, suggesting that the toxin had worked.

The action of BTXA is said to be confined to the presynaptic terminals of the peripheral nervous system that release acetylcholine, with no destruction of the motor end terminals.⁴ Previous observations on animal material have not shown nerve fibre damage similar to what we found, and only minimal muscle damage.⁵ Spencer and McNeer⁶ have reported hypertrophy in the orbital fast muscles and reduced vascularity 14 days after botulinum injection. These fibres later faded before returning to normal. There was little change in other fibre types. In contrast our results showed more generalised muscle changes, with inflammatory vascular changes, which are more likely to be due to the tissue hypoxia from the fistula. Duchon¹ has noted that slow fibres are affected earlier and recover more quickly after botulinum injection. We know that recovery does take place in man and experimental animals, and these differences may simply illustrate different times along the natural recovery pathway.

The apparent damage to the myelinated nerve fibre axons has not been reported by other

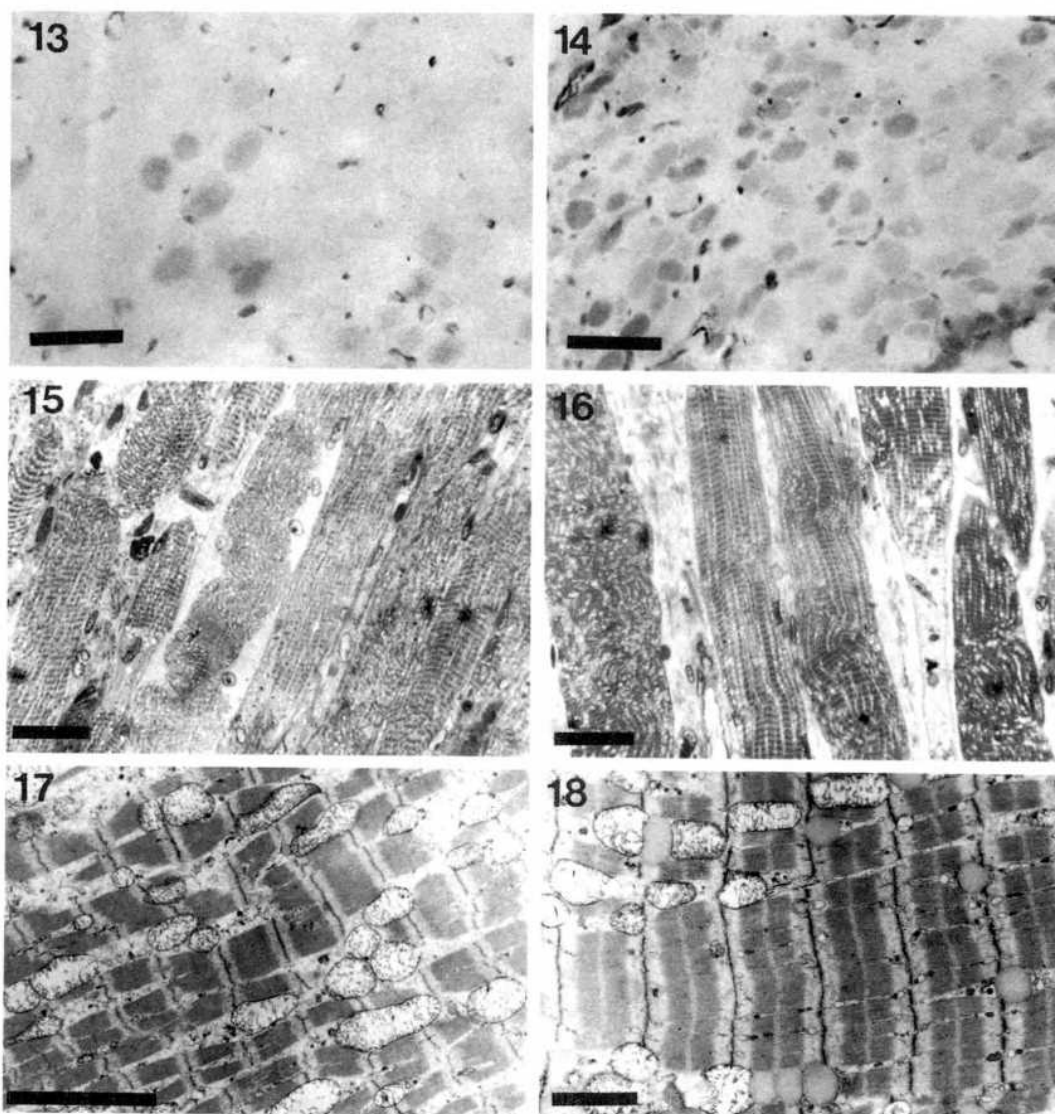


Figure 13 BTXA levator muscle, showing reduced staining of muscle fibres. (ATPase with preincubation at pH 4.3, bar=100 μ m.)

Figure 14 Normal levator muscle. (ATPase with preincubation at pH 4.3, bar=100 μ m.)

Figure 15 BTXA levator muscle, to show snake-like pattern with the muscle fibres coming away from the sarcolemma. (Toluidine blue, bar=25 μ m.)

Figure 16 Normal levator muscle. (Toluidine blue, bar=25 μ m.)

Figure 17 BTXA levator muscle. (Electron microscopy, bar=5 μ m.)

Figure 18 Normal levator muscle. (Electron microscopy, bar=2 μ m.)

workers. It is possible that this contrast with our observations is due to transient changes that are followed by a full morphological recovery. Our case is complicated by the dual pathology of a carotico-cavernous fistula and botulinum injections. Little has been reported on the effects of carotico-cavernous fistula on the extraocular muscle, though they are known to cause anoxic damage. Thus some of our observations may be due to ischaemic pressure necrosis from thrombosis and not just BTXA poisoning.

The authors are grateful to Dr S Dilly and Ms C Cope for expert technical assistance, and to Professor L Duchon, Dr A McCartney, and Dr P Wilkins for helpful comments on the pathological specimens.

- 1 Duchon LW. Changes in the electron microscopic structure of slow and fast skeletal muscle fibres of the mouse after the local injection of botulinum toxin. *J Neurol Sci* 1971; **14**: 61-64.
- 2 Sanders MD, Hoyt WF. Hypoxic ocular sequelae of carotid-cavernous fistulae. *Br J Ophthalmol* 1969; **53**: 82-97.
- 3 Spencer WH, Thompson HS, Hoyt WF. Ischaemic ocular necrosis from carotid-cavernous fistula. *Br J Ophthalmol* 1973; **57**: 145-52.
- 4 Duchon LW. Changes in motor innervation and cholinesterase localisation induced by botulinum toxin in skeletal muscle of the mouse: differences between fast and slow muscles. *J Neurol Neurosurg Psychiatry* 1970; **33**: 40-54.
- 5 Duchon LW, Strich SJ. The effects of botulinum toxin on the pattern of innervation of skeletal muscle in the mouse. *Q J Exp Physiol* 1968; **53**: 84-9.
- 6 Spencer RF, McNeer KW. Botulinum toxin paralysis of adult monkey extraocular muscle. *Arch Ophthalmol* 1987; **105**: 1703-11.

Bilateral homonymous visual field defects as initial manifestation of multiple sclerosis

Bernardo Sanchez-Dalmau, Francisco J Gofii, Mercè Guarro, Carles Roig, Francesc Duch-Bordas

Abstract

Symptomatic suprageniculate lesions in multiple sclerosis expressed as a visual field defect are infrequent. The present case developed a bilateral homonymous defect as the initial and unique symptom of the disease. It was confirmed by nuclear magnetic resonance imaging, which disclosed extensive demyelinating areas in both optic nerve radiations. The mode of onset, perimetric findings, and unusual presentation of this condition are briefly discussed.

Symptomatic retrochiasmal disease of the visual pathways in multiple sclerosis (MS) is unusual. An incidence of 1.3-3.5% of homonymous defects has been reported in several series.¹⁻⁴ However, much higher frequencies of retrochiasmal lesions have been found in neuroradiological examinations⁵ and necropsies⁶⁻⁸ without associated clinical manifestations. To our knowledge only one case of clinical simultaneous bilateral retrochiasmal involvement, expressed as a bilateral homonymous hemianopic defect, has been reported.³ This case was not studied by CT or nuclear magnetic resonance imaging (NMR).

We report a case that developed a symptomatic simultaneous bilateral homonymous defect as the initial and unique manifestation, examined by CT, NMR, and computerised static perimetry.

Case report

A 24-year-old woman was admitted to our hospital in July 1989. A fortnight before that she had been seen because of blurred vision. Her visual acuity was 1.0 (6/6) in each eye. The pupillary reactions, ocular motility, and findings on funduscopy examination were all normal in both eyes. Systemic and neurological examinations also gave normal results. Screening computerised perimetry (Short test program, Octopus 500 EZ) showed a congruous left superior quadrantanopic defect and a less delimited depression in the right inferior quadrants, deeper for the left eye. A week later she experienced paraesthesiae in her right upper limb.

On admission to hospital the neurological examination showed isocoria, slightly decreased pupillary reactions without evidence of afferent pupillary defect, and a symmetrical horizontal gaze nystagmus. Funduscopy examination was normal in both eyes. No other neurological symptoms were found. Screening perimetry disclosed a similar visual field loss pattern to that

seen on the first occasion (Fig 1). The results of biochemical, haematological, immunological, and serological blood tests were all normal. A lumbar puncture yielded clear colourless cerebrospinal fluid (CSF). The fluid contained neither red nor white cells; glucose and protein values were within the normal range; immunoglobulin levels were normal, but an IgG λ homogeneous component was detected. Microbiological and serological studies of the CSF gave negative results. A chest x ray was normal.

A CT scan of the brain performed without contrast material revealed hypodense, poorly defined lesions. The NMR disclosed extensive

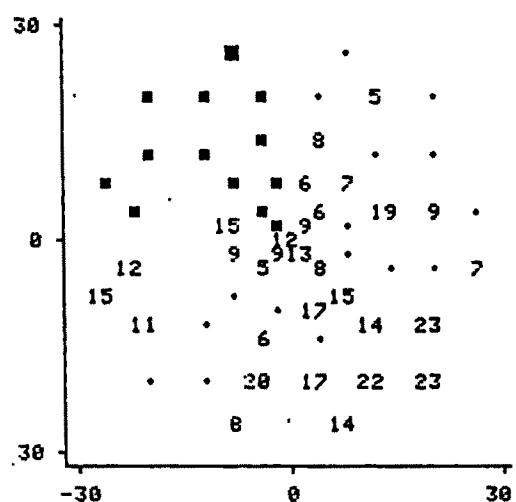
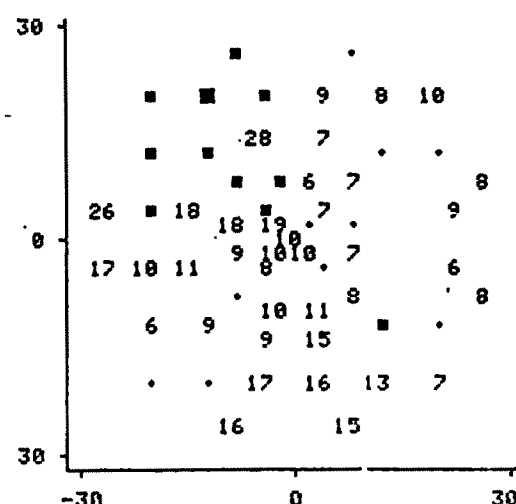


Figure 1 Computerised static perimetry (Short test program, Octopus 500 EZ) of right eye (top) and left eye (bottom), showing congruous left superior quadrantanopic defects and less delimited decreased thresholds in the right inferior quadrants. The remaining quadrants are only relatively spared, expressing deep disease of the suprageniculate visual pathways.

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Figures 2 A, B Axial T2-weighted magnetic resonance imaging of the optic radiations at different levels showing left and right extensive plaques on initial examination on July 1989.

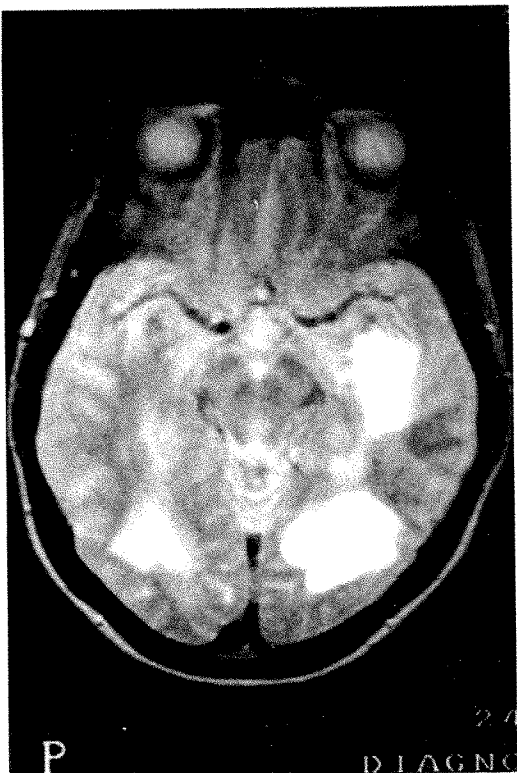


Figure 2A

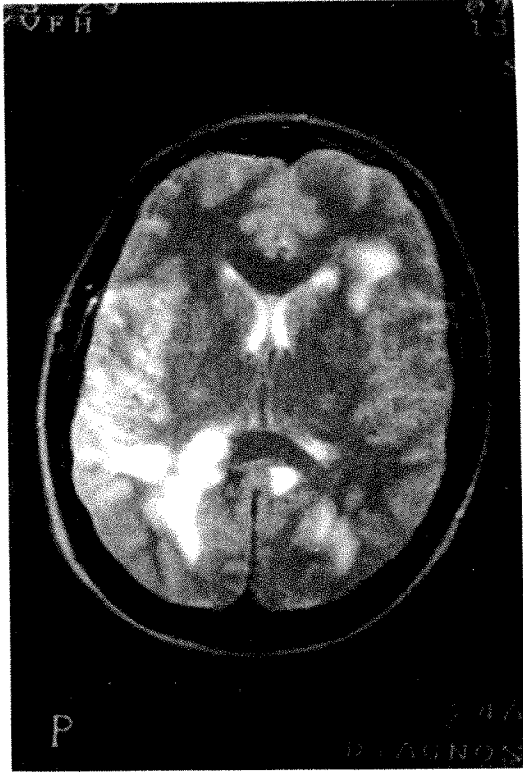


Figure 2B

bilateral frontal, occipitoparietal, and occipito-temporal areas of decreased density (Fig 2). Pattern visually evoked potentials (VEPs) showed abnormally increased latencies of the major positive wave (P-100) in both eyes. In hospital the patient had an attack of paresis of the right upper limb with pyramidal symptoms and bilateral impairment of deep sensibility with left predominance, associated with behaviour disorders and psychomotor agitation.

A diagnosis of probable MS according to the classification of McAlpine⁹ was made and treatment with methylprednisolone was started, with clinical and neurological improvement. The patient was discharged a few days later. After three months, when she was seen in the clinic, a new threshold perimetry performed with the G1 program showed a change of visual field loss pattern. Visual field indices were abnormal and a deep depression still remained. Six months after admission to hospital another perimetry showed

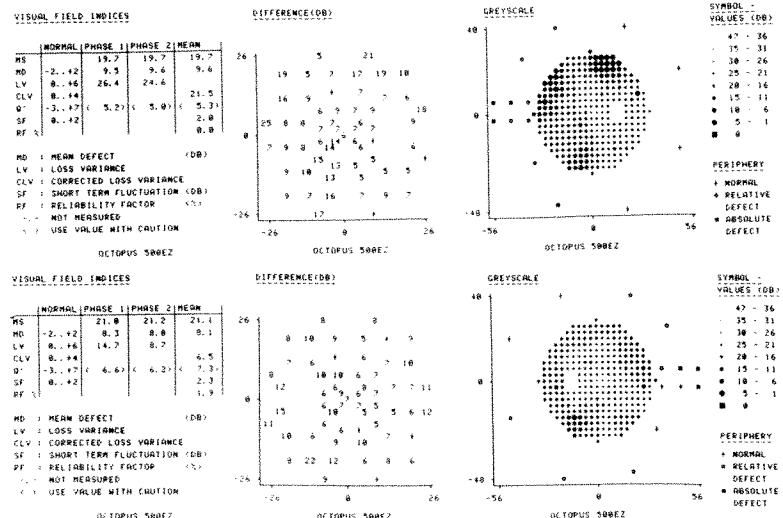
some improvement but still with abnormal indices (Fig 3). At that time another NMR revealed a marked reduction of white matter lesions (Fig 4).

Discussion

The onset of MS as homonymous hemianopia due to a supragenicular lesion of the visual pathways is extremely rare. Beck *et al*¹⁰ reported two cases, one of them without associated neurological symptoms at the onset. Even rarer is the condition of simultaneous bilaterality. Hawkins and Behrens³ reported the first case of a simultaneous bilateral homonymous hemianopia but late in the course of the disease. Our patient developed a bilateral visual field defect as the initial and unique manifestation, well characterised by computerised perimetry. It showed a congruous left superior quadrantanopic defect which seemed probably correlated with the right occipital lesion seen in the NMR. The right inferior quadrantanopic depression was less definite, but it was probably produced by a left parieto-occipital plaque. The 10 central degrees of the visual fields were relatively spared (they were mainly seen at the three months perimetry) in accordance with the good visual acuity. In fact supragenicular lesions produce a deeper defect in the midperiphery than in the central visual field.¹¹ This case showed a correlation between visual and neuroradiological findings, since improvement on perimetric examination concurred with a marked reduction of plaques in the NMR at the six months appointment.

It is difficult to say why symptomatic supragenicular lesions are so unusual in MS. The majority of lesions appearing as arcs of temporo-occipital white matter are clinically silent, as reported by Jacobs *et al*.⁵ On the other hand, many MS patients with no history of visual

Figure 3 A six months computerised perimetry (G1 program, Octopus 500 EZ) of right eye (top) and left eye (bottom), showing significant improvement of thresholds in both eyes, on the table of difference values. The grey-scale tables still depict localised scotomas on the border of the central fields.



Figures 4 A, B Axial T2-weighted magnetic resonance imaging at different levels on the six months examination showing marked reduction of bilateral white matter lesions.

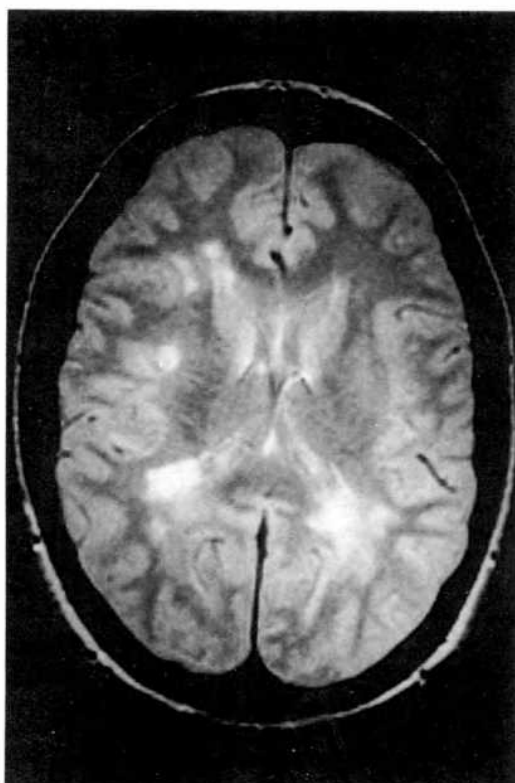


Figure 4A

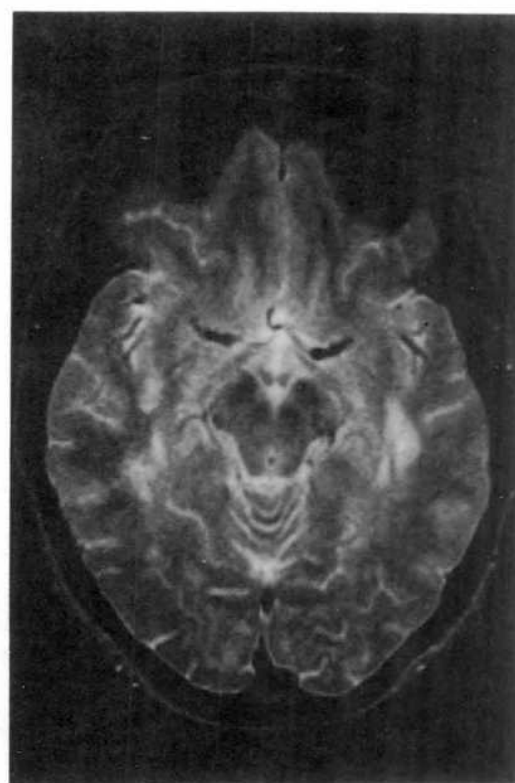


Figure 4B

symptoms have abnormal visual fields.^{12 13} Most of these abnormalities are probably related to subclinical optic neuritis, but some might be produced by lesions elsewhere than in the optic nerves, including the optic radiations. Thus supragenulate lesions are likely to be expressed as a subclinical manifestation rather than a symptomatic visual disturbance, as Hawkins and Behrens discussed.³ The high sensitivity of threshold static perimetry should be a valuable aid in the better characterisation of these conditions.

- 1 Kurtzke JF, Beebe GW, Nagler B, et al. Studies on natural history of multiple sclerosis. *Acta Neurol Scand* 1968; **44**: 467-94.
- 2 Leinfelder PJ. Retrobulbar neuritis in multiple sclerosis. *Assoc Res Nerv Dis Proc* 1950; **28**: 393-9.
- 3 Hawkins K, Behrens MM. Homonymous hemianopia in multiple sclerosis. *Br J Ophthalmol* 1975; **59**: 334-7.
- 4 Boldt HA, Haerer AF, Tourtellotte WW, Henderson JW, Dejons RN. Retrochiasmal visual field defects from multiple sclerosis. *Arch Neurol* 1963; **8**: 565-75.

- 5 Jacobs L, Kinkel WR, Polachini I, Kinkel PR. Correlations of nuclear magnetic resonance imaging, computerized tomography, and clinical profiles in multiple sclerosis. *Neurology* 1986; **36**: 27-34.
- 6 Savitsky N, Rangell L. The ocular findings in multiple sclerosis. *Assoc Res Nerv Dis Proc* 1950; **28**: 403-13.
- 7 Lehoczy T. Pathologic changes in the optic system in disseminated sclerosis. *Acta Morphol Hung* 1954; **4**: 395-408.
- 8 Lumsden CE. The neuropathology of multiple sclerosis. In: Vinken PJ, Brnyn GW, eds. *Handbook of neurology*. Amsterdam: North Holland, 1970; **9**: 217-309.
- 9 McAlpine D. In: McAlpine D, Lumsden CE, Acheson ED, eds. *Multiple sclerosis: a re-appraisal*. Edinburgh: Churchill Livingstone, 1972: 225.
- 10 Beck RW, Schatz NJ, Savino J. Involvement of the optic chiasm, optic tract and geniculocalcarine visual system in multiple sclerosis. *Bull Soc Belge Ophthalmol* 1983; **208**: 159-91.
- 11 Bynke H. A study of the depth of hemianopic field defects for optimizing computerized perimetry. *Neuro-ophthalmology* 1984; **4**: 237-47.
- 12 Patterson VH, Heron JR. Visual field abnormalities in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1980; **43**: 205-8.
- 13 Grochowicki M, Vighetto A. Etude du champ visuel per l'analyseur de Friedman Mark I et de la vision des couleurs chez 85 patients atteints de sclérose en plaques (SEP). Corrélation avec les PEV dans 50 cas. *J Fr Ophthalmol* 1988; **11**: 1:61-5.

Recurrent corneal oedema following late migration of intraocular glass

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Abstract

This is a report of very late complications following intraocular penetration of numerous fragments of glass as a result of a test tube explosion. Fifteen years after the initial injury glass splinters began to migrate from the vitreous into the anterior chamber, causing acute episodes of corneal oedema. Four such episodes occurred over the past nine years, the corneal oedema each time disappearing within a few days following surgical extraction of the glass splinters. The literature on intraocular glass and its movement within the eye is reviewed.

Penetration of glass splinters into the eyeball is much rarer than the penetration of metallic foreign bodies.¹ In about 4-7% of eye injuries there is involvement of glass,² with a similar percentage found in children.² According to Rathmann and Aertzi³ only one of 62 eye injuries by glass resulted in perforation, with glass retained within the eye. Unless it is photochromic glass is inert and does not cause any chemical reaction.³ Damage is due either to the original impact of the injury or to late secondary movement of the glass within the eye causing mechanical tissue damage.

There are few reports describing late spontaneous movement of intraocular glass fragments. The present report describes recurrent migration of glass splinters from the vitreous cavity into the anterior chamber, which started 15 years after the initial injury and continued intermittently over nine more years.

Case report

A 16-year-old school boy was admitted to our department on February 1965 because of bilateral perforating eye injuries caused by a chemical explosion of a glass test tube. Numerous glass splinters covered his face and chest. In both eyes the cornea was studded with splinters, which were also seen within the lens. An intumescent cataract developed in the left eye and was removed. This eye regained full visual acuity (6/6).

In the right eye the lens absorbed spontaneously, and only needling of the posterior capsule was eventually required. Because of pigmentary changes in the macula, vision in this eye remained at 6/20. Four years after the initial injury no posterior vitreous detachment could be seen, but a localised flat retinal detachment was diagnosed in the upper nasal quadrant. Numerous immobile glass splinters could be seen within the vitreous of the eye, and these did not cause any disturbance for about 15 years. However,

during all this time glass splinters were extruded from both corneae, with small corneal erosions and short episodes of tearing and pain.

In 1980 there was the first episode of severe corneal oedema in the right eye. Gonioscopy revealed two glass fragments, 2-3 mm in diameter, within the lower part of the angle. When the patient was prone these fragments were seen to lie free on the corneal endothelium. Both fragments were surgically removed through a limbal incision, and thereafter up to December 1988 the patient underwent three more similar operations with removal of glass from the anterior chamber angle, always because of recurrence of moderate to severe corneal oedema. After each of the four operations the oedema disappeared completely within two to five days.

When last seen in June 1989, the right eye was quiet and the cornea was clear, with minute glass splinters within the stroma. The anterior chamber was deep. The pupil was slightly irregular but reacted normally. There was aphakia with a large central opening in the posterior capsule. The vitreous, which showed advanced syneresis, contained numerous glass splinters distributed both anteriorly and posteriorly within it. The flat retinal detachment in the upper nasal quadrant remained unchanged. The disc was normal, and there were old pigmentary changes in the macular area. Vision remained 6/20 with aphakic correction.

In the left eye no further changes have occurred, and vision remained 6/7 with aphakic correction.

Discussion

Cases in which glass splinters penetrate the eye are relatively rare owing to the low weight of glass. In most cases glass penetrates the eyeball as a result of an explosion, in which the high kinetic energy compensates for the low weight. More rarely penetration is due to broken spectacle lenses, window panes, etc.

Cutko (quoted by Milkowski²) collected 100 cases with retained intraocular glass fragments which were seen between 1942 and 1960. In the majority, 73 eyes, the localisation was within the anterior chamber; in the remaining cases the fragments were described within the lens, ciliary body, vitreous, retina, and choroid.

Unlike other intraocular foreign bodies, glass tends to be localised within the anterior segment of the eye. Fragments in the posterior segment are relatively immobile and usually less injurious. Cohen⁴ described a glass fragment stuck in the retina, remaining asymptomatic over a period of 28 years. Santoni¹ described a fragment of glass near the disc remaining asymptomatic over a period of 11 years; while another fragment from

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the same injury caused episodes of bullous keratitis for three years until it was discovered and removed from the anterior segment. Glass fragments may remain for years within the lens and cause only minimal local cataract.⁵

There are rare reports of late migration of glass fragments from the posterior to the anterior segment of the eye. Löhlein⁶ described migration from the ora serrata causing traumatic cataract five years after the original injury, when the glass eventually found its way into the anterior chamber. Cutko (quoted by Milkowski² described migration of a fragment from the posterior chamber into the anterior chamber, which occurred six weeks after the injury. Cauer⁷ described a fragment which was stuck between the sclera and ciliary body remaining asymptomatic for 23 years and was then found in the anterior chamber.

Migration of intraocular glass is always from the back forwards and, in 85% of the cases, also downwards.² The last direction of movement is easily understood, since glass is heavier than aqueous. It is more difficult to explain the forward movement, and various factors need be considered. Simple dislocation of glass within the eye could be triggered or influenced by repeated trauma, sporting activities, or head and eye movements. The overall forward movement is probably influenced by intraocular flow of the aqueous. When splinters are retained within the lens they may fall into the anterior chamber as a result of a slow process of spontaneous absorption of the lens.

In cases of aphakia, especially after intra-capsular cataract extraction, splinters can more easily move from the posterior to the anterior segment. In the present case there were large openings in the posterior capsule that allowed such movement already within the first year following the injury. The fact that glass splinters started to appear in the anterior chamber and

caused corneal oedema 15 years after the initial injury is probably due to the slow and progressive liquefaction of the vitreous over this period of time.

The tendency to vitreous liquefaction increases with age and probably occurs sooner and more often following trauma that involves the posterior segment of the eye. In the present case the initial injury occurred at the age of 16, and vitreous liquefaction was sufficiently advanced to allow migration of glass from it into the anterior chamber at the age of 31. So far no late injury has occurred within the posterior segment from the free movement of glass within the vitreous. The late, localised, flat retinal detachment in the right eye appeared relatively early, did not progress over the years, and no retinal tear could be found. Probably it resulted from vitreous traction following the original injury. At the time of the initial injury, in 1965, as well as four years later when the localised detachment was diagnosed, vitrectomy did not exist. Later on it was considered when fragments of glass migrated into the anterior chamber, causing corneal oedema. However, in view of the very large number of glass splinters within the vitreous this procedure seemed to be risky, especially in the presence of a localised retinal detachment that has not progressed over a long time.

- 1 Santoni A, Sulle conseguenze della ritenzione dei frammenti di vetro nell'interno dell'occhio. *Boll Oculist* 1958; 37: 81-8.
- 2 Milkowski S. A rare case of spontaneous shifting of intra-ocular glass foreign body 21 years after trauma. *Wiad Lek* 1978; 31: 1065-9.
- 3 Rathmann GZ, Aertzi Z. Studies on the causes of eye injuries due to glass jars and the possibility of their avoidance. *Fortbild* 1962; 56: 1008-14.
- 4 Cohen M. Glass embedded in the eye. *Arch Ophthalmol* 1929; 1: 528-9.
- 5 Richards WW, Arrington JM. Asymptomatic intralenticular glass fragment. *Am J Ophthalmol* 1969; 67: 375-7.
- 6 Löhlein W. Bemerkungen zur operativen Indikationsstellung bei intraokularen Fremdkörpern (Kupfer, Eisen, Glas) in letztem Auge. *Klin Monatsbl Augenheilkd* 1951; 119: 113-21.
- 7 Cauer R. 23 Jahre im Augeninnern wandernder Glassplinter. *Klin Monatsbl Augenheilkd* 1941; 106: 91-4.

Bilateral retinal hamartomas in neurofibromatosis type 2

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Abstract

We report a case of bilateral retinal hamartomas in a child with neurofibromatosis type 2. This unique case demonstrates that a diversity of retinal changes can occur in this disease.

Neurofibromatosis (NF) consists of at least two genetically and clinically distinct types, NF-1 (von Recklinghausen's type) and NF-2 (acoustic neuroma type).¹ Gene defects on chromosome 17 are responsible for NF-1. A loss of genes on chromosome 22 causes NF-2.

Cotlier reported a combined pigment epithelial and retinal hamartoma (CPRH) in a patient who, in retrospect, had NF-2.² Landau

et al reported the possible association of the CPRH with NF-2 in another patient.³ We report another case of bilateral hamartomas in a patient with NF-2.

Case report

A 7-year-old boy was admitted to the University of California San Francisco Neurosurgery Service for evaluation of hemiatrophy and fasciculation of the right side of the tongue. He had one café-au-lait spot and diminished hearing on the right. His mother, grandmother, and two aunts were afflicted with neurofibromatosis and bilateral acoustic neuromas. A CT scan showed a partially calcified mass in the right cerebellopontine angle. At surgery a large meningioma of the cerebellopontine angle was subtotally resected. Histologically it was found to be malignant. Neurofibromas of cranial nerves 11 and 12 and a second meningioma extending through the hypoglossal canal were also noted.

Exotropia had been surgically corrected at age 2. Visual acuity was 20/800 in the right eye and 20/20 in the left. Right esotropia was present, with ductions full. In the right fundus (Fig 1) there was a lesion involving the optic nerve head and macula. The lesion was bordered by a rim of subretinal fibrosis with a diaphanous glial membrane in its centre. Retinal vessels were pulled towards the lesion. The left retina contained multiple 1/4 to 1/2 disc diameter areas of presumed glial proliferation on the inner surface of the retina. These lesions were located infero-temporally and obscured underlying retinal vessels in some areas. They caused a distorted light reflex from the inner surface of the retina.

Discussion

Our patient had multiple cranial nerve tumours and meningiomas, and a family history of bilateral acoustic neuromas. He was afflicted with the genetic defect that causes NF-2. The CPRH lesions in NF-2 patients reported by Cotlier² and by Landau *et al*³ are similar. Our case is quite different and exemplifies a diversity of retinal changes that can be found in NF-2.

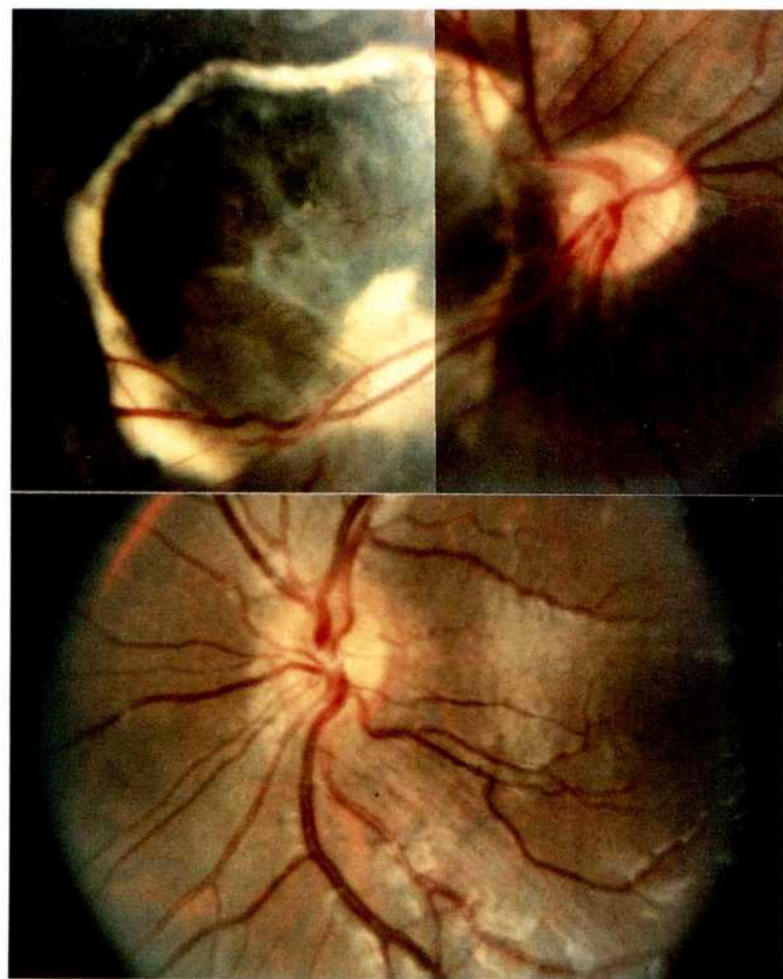


Figure 1 Above: Right eye, lesion involving optic nerve head and macula. Below: Left eye, areas of presumed glial proliferation on inner surface of retina.

1 National Institute Health Consensus Development Conference Statement of Neurofibromatosis. *Arch Neurol* 1988; 45: 575-8.

2 Cotlier E. Café-au-lait spots of the fundus in neurofibromatosis. *Arch Ophthalmol* 1977; 95: 1990-2.

3 Landau K, Muci-Mendoza R, Dosssetor F M, Hoyt W F Retinal hamartoma in neurofibromatosis 2. *Arch Ophthalmol* 1990; 108: 328-9.

LETTERS TO THE EDITOR

Axial length measurement discrepancies in asteroid hyalosis

SIR,—Axial length (AL) measurement is the most important factor affecting intraocular lens (IOL) power calculations. A difference of 1 mm in axial length will affect the postoperative refraction by approximately 2.5 dioptres. The ophthalmologist should therefore be aware of factors which will yield spurious measurements. These factors include posterior pole colobomas, posterior vitreous detachments, macular oedema, and others.¹ Asteroid hyalosis (AH) is generally not expected to affect AL measurements. A review of the literature provided only one case report of falsely decreased AL measurement secondary to AH necessitating a second IOL implantation.²

Asteroid hyalosis is an uncommon condition occurring most frequently in elderly individuals in the 7th and 8th decades. It appears as a myriad of tiny spherules containing calcium and phospholipids suspended throughout the vitreous. It is usually unilateral, has no sex predilection, and has not been definitively associated with systemic or ocular disease.³

We present a case in which asteroid hyalosis in a cataractous eye falsely lowered the axial length measurement, yielding an incorrect IOL power calculation. Implantation of this lens would have resulted in a significant refractive error. We studied the axial length measurements in five additional cases with asteroid hyalosis to compare measurements with predicted estimates.

A 52-year-old black diabetic female had been followed up by her retinal specialist for macular oedema OS. Examination of the left eye was remarkable for a visual acuity of 20/400 with a -1.00 sphere, a moderate nuclear sclerotic cataract, severe macular oedema, and asteroid hyalosis. The right eye had a posterior chamber IOL and was emmetropic, with a visual acuity of 20/25. Asteroid hyalosis was present OD, but ophthalmoscopic examination gave otherwise normal results.

An A scan was performed with the Cooper ABX 1000 and yielded AL measurements of 22.00 mm OD and 22.10 mm OS. The measurements were reproducible and resulted in an IOL power calculation of +24 D (SRK II regression formula) for both eyes. Since the average AL is 23.5 mm, these readings would be consistent with a hyperopia of 4 dioptres. However, the patient's elicited refractive history, current visual acuity, and results on ophthalmic examination were not consistent with such a degree of hyperopia. In addition, the pseudophakic eye had received a +20.50 dioptre IOL (not 24.0 D) and had achieved emmetropia. We concluded that the AL measurement in both eyes was spuriously decreased secondarily to AH. Based on our clinical impression a +21.50 IOL was implanted OS instead of the calculated +24.0, with a resultant postoperative refraction of plano.

Our case report describes artefactual lowering of the AL measurement in a patient with AH. Except for the above mentioned report²

AH has not previously been known to affect AL measurements. In our case macular oedema may have been a contributing factor in spuriously decreasing AL in the left eye. The right eye, however, had asteroid hyalosis without macular oedema but still had artefactual lowering of the AL measurement.

Owing to these findings we examined five patients who had a history of unocular AH without any other ocular abnormality. Retinoscopic readings, keratometry, current visual acuity, and refractive history were all studied. An A scan was performed with the Cooper ABX 1000. Four of the five patients had predictable AL measurements consistent with their history and findings on examination. One patient, however, had an AL which measured 2.5 mm shorter than predicted in the eye with AH. A difference of this magnitude from the expected AL is extremely unusual.

Although no formal study has been undertaken on this issue, we believe strongly that asteroid hyalosis can cause artefactual lowering of axial length measurements. Careful consideration of the refractive history and clinical examination may avert implantation of an erroneous lens.

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- 1 Schecter RJ. Optics of the intraocular lenses. In: Duane TD, ed. *Duane's clinical ophthalmology*. Philadelphia: Lippincott, 1989: 3-4.
- 2 Martin RG, Saffir A. Asteroid hyalosis affecting the choice of intraocular lens implant. *J Cataract Refract Surg* 1987; 13: 62-5.
- 3 Tasman W. The vitreous. In: Duane TD, ed. *Duane's clinical ophthalmology*. Philadelphia: Lippincott, 1989: 11.

Diabetes and retinal function

SIR,—We were interested in the recent article by Bek and Lund-Andersen¹ and in your accompanying editorial.² It is true that much has been published in recent years concerning the vascular aspects of diabetic retinopathy. The earliest changes in diabetic retinopathy need not, however, be vascular. Thus, Bek and Lund-Andersen could not demonstrate areas of visual field loss corresponding to retinal hard exudates or fluorescein leakage, but this may be because their test of retinal function was not sufficiently sensitive. A similar study using a more sensitive test of retinal function such as S cone pathway sensitivity³ or luminance or chromatic threshold measurement⁴ might increase the likelihood of detecting differences in function between an area of apparently normal retina and an adjacent area where a breakdown in the blood-retinal barrier is obvious.

Although a breakdown in the blood-retinal barrier may precede neurosensory dysfunction as suggested by Bek and Lund-Andersen, recent work in our laboratory suggests the opposite may be true. We compared 36 patients with insulin-dependent diabetes with 36 age-matched controls. Funduscopy, fundal photography, and fluorescein angiography confirmed that none of the diabetics had breakdown of the blood-retinal barrier, but colour vision assessed by the Farnsworth-Munsell 100-hue test was markedly abnormal in the diabetic group compared with normal controls (mean FM 100-hue error score for diabetics

85.2 (SEM 7.6) v 29.5 (SEM 3.3) for controls, $p < 0.001$).

We believe the question of whether vascular or neurosensory dysfunction occurs first in diabetic retinopathy remains open.

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- 1 Bek T, Lund-Andersen H. Localised blood-retinal barrier leakage and retinal light sensitivity in diabetic retinopathy. *Br J Ophthalmol* 1990; 74: 388-92.
- 2 Smith R. Diabetes and retinal function. (Editorial). *Br J Ophthalmol* 1990; 74: 385.
- 3 Greenstein V, Sarter B, Hood D, Noble K, Carr R. Hue discrimination and S cone pathway sensitivity in early diabetic retinopathy. *Invest Ophthalmol Vis Sci* 1990; 31: 1008-14.
- 4 Foster DH, Snelgar RS, Heron JR. Nonselective losses in foveal chromatic and luminance sensitivity in multiple sclerosis. *Invest Ophthalmol Vis Sci* 1985; 26: 1431-41.

Reply

SIR,—The question of which measure of retinal function is the best of course depends on what one wishes to study. What I think is important, however, is that perimetric light sensitivity in practice appears to reflect clinically significant visual loss. Therefore the relation between perimetric results and extrafoveal morphology may help us to learn which morphological lesions in the foveolar area may lead to lowered visual acuity. In this context the most important finding described in the paper might perhaps be the lack of correlation between fluorescein leakage and loss of retinal light sensitivity. The reason why some hard exudates do not produce visual field scotomata is probably that this lesion causes considerable light scattering, a phenomenon that can be directly observed with the scanning laser ophthalmoscope.

I agree that some subclinical measure of retinal neurosensory impairment may perhaps be the initial sign of retinopathy. However, I don't think that the reduced blue-sensitivity of diabetic patients that has been known since the 1960s¹ is necessarily an argument in favour of this hypothesis. It has been shown that the lens browning (nuclear sclerosis) of diabetic lenses is higher than in normals, increasing with age² and with poor metabolic control.³ This lens browning causes increased lens autofluorescence, absorption, and light scattering, and thereby less light transmission, especially in the blue-green area, an effect that can account for the decreased blue sensitivity of these patients (Larsen *et al*, in preparation: (personal communication)). Therefore I think that an evaluation of colour vision anomalies of diabetic patients at least requires a proper correction for the individual wavelength-dependent light loss in the refractive media (notably the lens) due to autofluorescence, absorption, and scatter.

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- 1 Kinnear PR, Aspinall PA, Lakowski R. The diabetic eye and colour vision. *Trans Ophthalmol Soc UK* 1972; 92: 69-78.

- 2 Bleeker JC, van Best JA, Vrij L, van Velde EA, Oosterhuis J. Autofluorescence of the lens in diabetic and healthy subjects by fluorophotometry. *Invest Ophthalmol Vis Sci* 1986; 27: 791-4.
- 3 Larsen M, Kjer B, Bendtsen I, Dalgaard P, Lund-Andersen H. Lens fluorescence in relation to metabolic control of insulin-dependent diabetes mellitus. *Arch Ophthalmol* 1989; 107: 59-62.

A light pipe guard to prevent iatrogenic retinal injury during vitrectomy

STR. — Iatrogenic retinal injury has occurred in 38% of eyes undergoing vitrectomy for progressive proliferative diabetic retinopathy.¹ An iatrogenic break worsens the visual prognosis.² It is therefore essential to make every effort to avoid such injuries. One preventable cause is retinal injury due to the fiberoptic light pipe. This can be avoided by using it with a guard to prevent excessive introduction. The light pipe length is excessive, 35 mm, and compares unfavourably with the average chord lengths: from pars plana port to macula of 22 mm, or to the proximal retina 16 mm (if a path parallel to the visual axis is taken).



Figure 1: The (35 mm) light pipe is covered at its proximal end with 20 mm of tarsorrhaphy tubing to guard against excessive introduction of the light pipe into the eye.

In order to minimise the risk to the retina we have restricted the introduction of the light pipe to 15 mm by covering the proximal pipe with a 20 mm length of tarsorrhaphy tubing (Fig 1). In this way it is impossible to introduce the light pipe far enough to injure the macula and yet it goes far enough to remain in view even if the pupil is not well dilated. This precaution will keep the tip 8-10 mm from the retina for most of the tip's arc of movement within the eye.

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- 2 Thompson JT, Auer CL, Bustros S de, Michels RG, Rice TA, Glaser BM. Prognostic indicators of success and failure in vitrectomy for diabetic retinopathy. *Ophthalmology* 1986; 93: 290-5.

BOOK REVIEWS

Clinical Tests: Ophthalmology. By M J E Huber, M H Reacher. Pp 176. £25.00. Wolfe Medical: London, 1990.

This is a beautifully illustrated book, but really I am at a loss to comprehend just at which market it is being aimed. I have not had the

opportunity to look at others in the series of Wolfe Medical Atlases. There are 244 excellent photographs, but, for instance, on gonioscopy (pp. 114-7) there are five pages of non-useful pictures, then two of angles of the anterior chamber, but no legend as to what is being viewed in the angle photographs.

There are 15 pages on field testing – the majority as provided by the instrument manufacturer – and the fields which are printed again have no explanatory caption. Photograph 58 on exophthalmometry has a legend which is somewhat inaccurate, and illustration 16 on infant restraint is hardly likely to commend itself for help in primary care practice.

The presentation is excellent and the printing is superior to many other more useful publications, but I do not really see what addition it is to the voluminous range of titles already available. As claimed on the cover, this is an uncomplicated guide to testing of eye status, but I do not think optometrists would find much in the book of value, and for ophthalmologists there is really no information of use for revision, for practical or theoretical learning, or to recommend to practitioners interested in the specialty.

WILLIAM M DOIG

A Colour Atlas of Ptosis: A Practical Guide to Evaluation and Management. By J J Dutton. Pp 156. No price given. PG Medical Books: Singapore. 1989.

This book sets out to present a simple, concise, and well illustrated guide to ptosis surgery specifically directed at the surgeon who is less familiar with eyelid anatomy and who does not perform such operations on a daily or weekly basis. A logical classification based on the aetiology of ptosis is first presented with excellent photographs illustrating many different causes of it. Surgical anatomy is then covered with very clear, concise diagrams. The third chapter discusses preoperative evaluation, and the next four chapters detail the author's techniques for a modified Fasanella Servat procedure, aponeurosis repair, anterior approach levator resection, and brow suspension. The surgery is presented with a matching series of operative photographs, diagrams, and explanatory captions which are incredibly clear and easy to follow. The actual text is kept to a minimum and supplements the operative series excellently. It is well laid out under the clear headings of anaesthesia, surgical technique, postoperative care, results, complications, and references.

It is extremely difficult to find anything to criticise in this book, and the author is to be congratulated on having produced the most beautifully clear and concise pictorial guide to ptosis that I have ever seen. Surgeons practising a lot of ptosis surgery may disagree with one or more minor details, such as the Iliff modification of the Fasanella Servat procedure, the lack of any mention of posterior approach aponeurosis and levator surgery, or the use of a buried non-absorbable suture for securing autogenous fascia lata used in a brow suspension operation. No book can cover all aspects of a subject, and this book has undoubtedly achieved the aim of being a simple, clear, illustrated guide to the main ptosis operations that any surgeon may want to use. It is without doubt the best guide to the subject that has yet been produced and cannot be warmly enough recommended to everybody who proposes to start ptosis surgery or who practises it infre-

quently and wants to refresh their memory prior to doing an operation.

J R O COLLIN

Ophthalmic Surgery: Principles and Practice. Edited by George L Spaeth. Pp. 755. £90.00. Saunders: London, 1990.

Edmund Spaeth, an ophthalmologist who practised general and ophthalmic plastic surgery in Philadelphia, USA, also wrote a surgical ophthalmic text which can now be seen as a precursor to that edited by his son George. The baton of this father and son team could have been said to have been handed over in 1971, when in a unique event in British ophthalmology both appeared on the same programme at the Oxford Congress.

Since that time Spaeth Jnr has continued to delight his ophthalmic audiences with both his spoken and his written word. We in the audience have come to expect to be educated both in the science but also in (a much less frequently tilled pasture) the philosophy of our craft. One achievement has been to bring both these facets together in this comprehensive text. The first edition appeared in 1982, and now, eight years later, the second.

This book sets out to cover all aspects of the surgeon's craft, from fundamental principles to basic elements of individual surgical procedures. In updating it the editor has kept the book at the same length as the first edition. New sections have been added on keratorefractive and laser surgery, while others have been either updated or extensively rewritten. It is copiously illustrated by means of black-and-white photographs and line drawings. Compactness of the text is maintained by means of numerous tables. Finally, chapters are concluded with (largely) up to date references.

The book represents the current practices of the American writers of the text. Even in a rapidly shrinking world some differences in practice still remain between colleagues on the American continent and elsewhere. The British reader should bear in mind that not all the possible approaches to a problem are necessarily listed, but can rest assured that those that are will be tried and tested and actually work. The book is affordable at today's prices, practical, and a worthwhile addition to every ophthalmologist's bookshelf.

R HITCHINGS

NOTES

Fourth Eupo course

The fourth Eupo course (European Community Professors of Ophthalmology) will be held in Turin on 20-22 June 1991. Details from Organising Secretariat, CIC Srl, C.so Stati Uniti 3, 10128 Torino, Italy.

Duke spring symposium

The Duke Eye Center Spring Symposium will be held on 16-18 May 1991 at the Omni Durham Hotel and Convention Center, Durham, North Carolina, USA. Further information from George Andrews, Duke Eye Center, Box 3802, Durham, NC 27710, USA.

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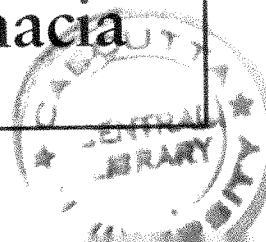
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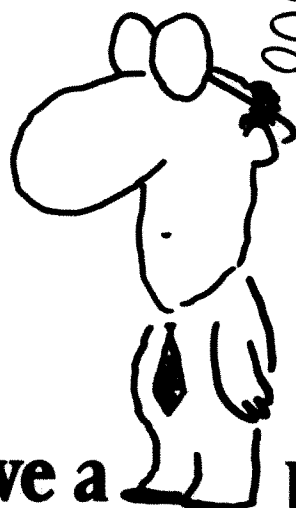
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1. Duzman, E. *et al.*, Am J Ophthalmol 1982; 94 (3): 318-327. 2. Rakofsky S.I. *et al.*, Ophthalmology 1989; 96 (1): 8-11. 3. Wandel, T. *et al.*, Am J Ophthalmol 1986; 101: 298-304.



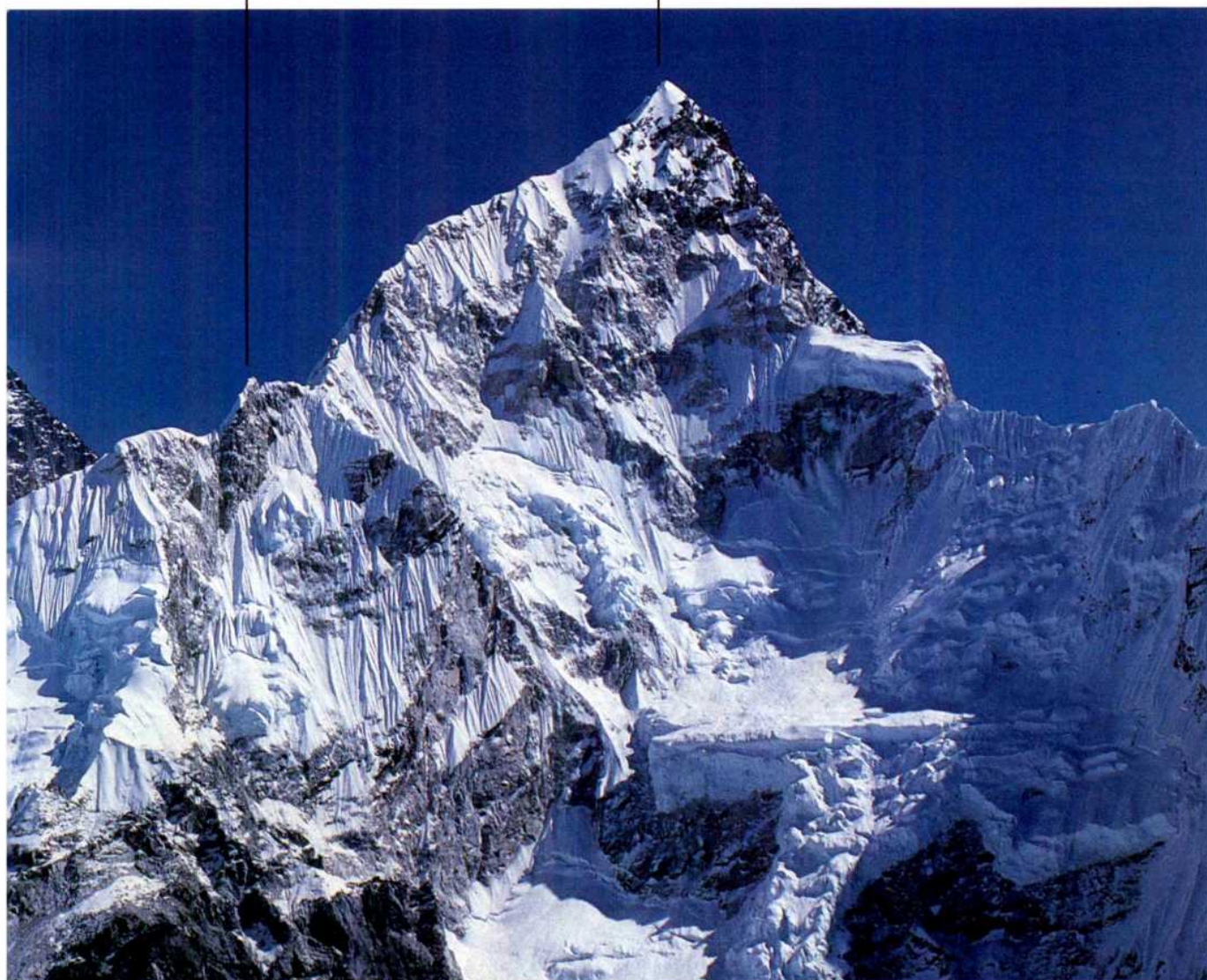
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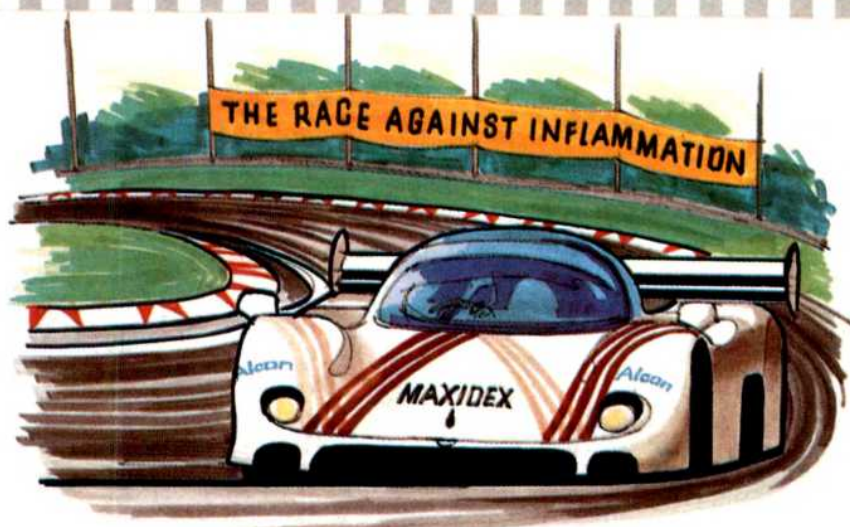
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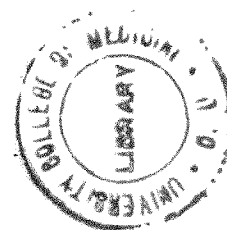
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BRITISH JOURNAL OF OPHTHALMOLOGY



Editorial

Molecular biology for the ophthalmologist?

Our knowledge of virological disease has expanded considerably over the past few decades subsequent to some remarkable developments in molecular biology. As each technique has been developed it has moved from a largely research orientated tool to its incorporation within the diagnostic regimen. Ophthalmologically related viral disease has not been immune from such developments. We therefore need to understand the implications and applications of these developments.

Since the discovery of DNA in 1869 and the realisation that DNA is a genetic molecule there has been an exponential growth in biological information. The isolation of DNA polymerase I in 1958 (an enzyme capable of making DNA in vitro), DNA ligase in 1967 (which joins together two DNA chains), and the first restriction enzyme (an enzyme which will cleave the DNA molecule at specific sites) allowed the joining together of DNA fragments created by a restriction endonuclease to form a recombinant DNA molecule. The successful isolation of many different restriction endonucleases that cut DNA at their specific base recognition sites has made it possible to detect changes (mutations) in a DNA sequence by the inability to cut at an expected position in the DNA molecule with a given endonuclease. For example, the restriction enzyme from *Haemophilus aegyptius* (Hae III) will cut the DNA wherever the sequence

GG*CC
CC*GG

occurs, leaving blunt ends to the fragments, whilst that from *Escherichia coli* (Eco RI) will cleave the DNA at and wherever the sequence

G*AATC
CTTA*G

occurs, leaving the DNA fragments with overlapping or sticky ends. (*Represents the position where the DNA is

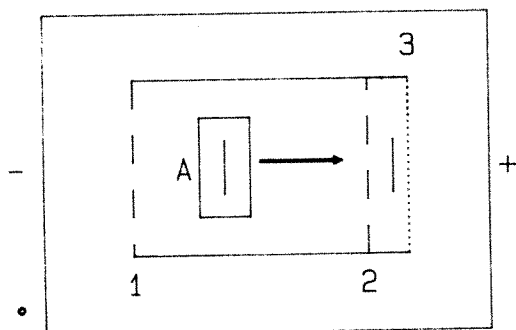


Figure 1 Electroelution. The band of DNA within the excised piece of gel (A), moves into the compartment between membranes 2 and 3.

cut. A=adenine; C=cytosine; G=guanine; T=thymine.)

The fragments generated when viral DNA is cut by an enzyme can be easily separated on gel electrophoresis by comparing the rate at which the fragments move under the influence of an electric current, with marker fragments of known molecular weight. The fragments of DNA can then be extracted from the gel by centrifugation, electroelution (Fig 1), or denatured and transferred to a membrane by capillary action (Figs 2) for further analysis. This can be done by hybridising the denatured DNA fragments to a labelled nucleic acid probe, which is complementary to the fragment under investigation – that is, Southern blotting¹ – or further digesting the extracted DNA fragments with a restriction endonuclease, as described by Kaye *et al* in the *BJO* this month. More definitively, the nucleic acid sequence of the fragments can be determined.

Techniques such as in situ hybridisation, whereby a labelled nucleotide probe of known sequence is hybridised to either RNA or denatured DNA within a preparation of tissue, have allowed the detection and localisation of the respective nucleic acid within the tissue or its components. Restriction endonuclease mapping has allowed the subtyping or straining of various viruses such as herpes simplex type 1 (HSV-1) into some of its component strains. This has clinical applications for the ophthalmologist both from epidemiological aspects and from the knowledge that some strains are clinically more virulent than others.

The concept of HSV latency within the trigeminal ganglion is well known. Here it is beyond the reach of conventional treatment. Support for the idea of corneal HSV latency arose from the isolation of HSV from the corneal discs of patients with previous herpes simplex keratitis by prolonged

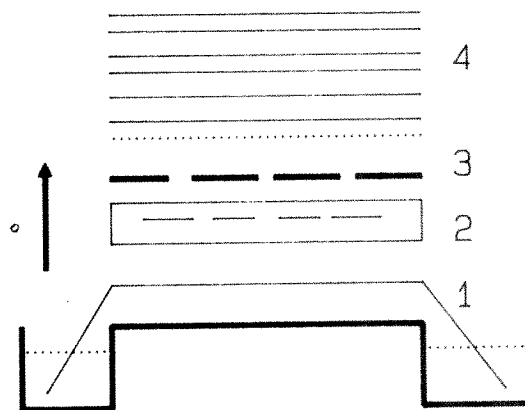


Figure 2 Absorbent towels (4) cause fluid to move up filter paper (1), through the gel (2), carrying denatured DNA bands on to membrane (3).

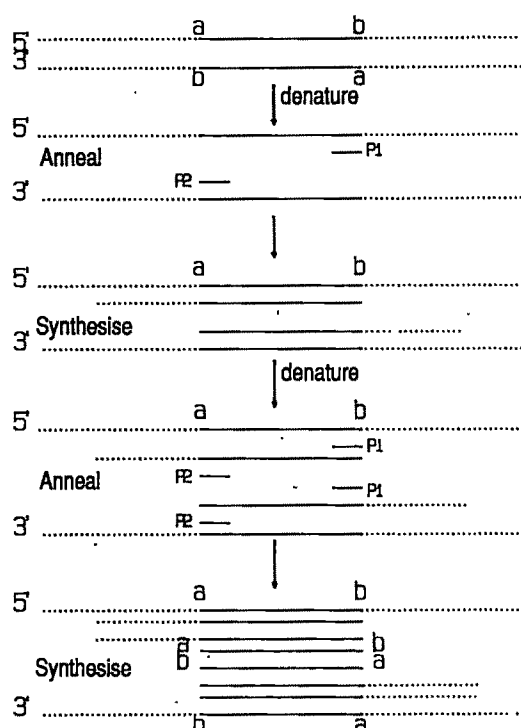


Figure 3 Polymerase chain reaction. *ab* represents segment of DNA which is amplified. Each cycle consists of denaturation of the DNA, annealing of the primers, P1 and P2 to the DNA and the subsequent synthesis of new strands. Segment *ab/ba* accumulates at an exponential rate by acting as its own template.

corneal explant culture.⁴ This then became a subject of much debate, the pursuit of which has been hampered by the very low levels of virus with which one may be dealing. Recent developments in molecular biology, however, of which the polymerase chain reaction³ (PCR) is a milestone, has made it possible to overcome this problem. This technique allows a sequence of DNA to be amplified from minuscule amounts of DNA, thus making it amenable to direct analysis.

The PCR is based on the repetitive cycling of three reactions (Fig 3). Each cycle consists of three steps: denaturation of the target DNA by heating to a high temperature, annealing of oligonucleotide primers to the target DNA, and the synthesis of two new strands of DNA by a DNA polymerase. If a sequence of RNA is to be amplified, a copy of it must first be made (cDNA) by a reverse transcriptase before beginning the PCR. The oligonucleotide primers used average 18 to 25 bases in length and can be easily synthesised with automated equipment. In practice two specific primers are used which flank the region of interest. One primer is complementary to the coding strand and the other complementary to the non-coding strand. Synthesis of the DNA occurs along both the coding and non-coding strands from the primer binding sites. As these steps are repeated, the DNA defined by the primers undergoes exponential amplification as the newly synthesised strands themselves become templates.

The discovery and subsequent cloning of the heat stable DNA polymerase of *Thermus aquaticus*⁴ has allowed automation of the procedure, so that it is possible to amplify specific DNA sequences more than a million-fold in the same tube in only a few hours. Because of this simplicity, the PCR has widespread applications from basic science and clinical research to the routine diagnosis of certain diseases, or even the amplification and sequencing of DNA from the brain of an ancient mummy.⁵ Furthermore the ability of the PCR to

detect as little as a single copy of a gene in 10^5 cells makes it particularly suited to the study of corneal latency. The definition of latency is based on an operational definition – that is, the absence of detectable virus from a cell-free suspension but the presence of virus following prolonged organ culture. Kaye *et al* have added to this definition (1) the demonstration of viral DNA; (2) the absence of viral transcripts produced in a productive infection; and (3) the presence of latency-associated transcripts (LATs), which, though not essential for the establishment or maintenance of latency,⁶ have been found in increased amounts in a latent infection. At present they do not appear to code for any known viral protein. (This definition will undoubtedly need further modification as the role of various viral transcripts coding for proteins such as IPCO, 4, and 27 become further defined.)

It is important therefore to consider whether these criteria have been met. Kaye *et al* demonstrated the presence of three pieces of HSV DNA well separated on the viral genome, which argues strongly for the presence of extensive stretches of the viral genome. In nine of the 15 corneas in which HSV DNA was demonstrated evidence for the presence of LAT, in the absence of glycoprotein C transcripts (a late viral protein expressed in a productive infection) was found. Although this is suggestive of a latent infection, the possibility remains that other areas of the viral genome were being transcribed which went undetected. Furthermore, although attempts to reactivate virus from the corneal discs by tissue cocultivation with and without azacytidine (a hypomethylating agent) were made, virus was not detected. This is unfortunate, as the ability to reactivate virus is an important prerequisite for demonstration of a latent infection. Nevertheless this work goes a long way in support of the concept of corneal latency.

The finding of viral DNA in five of 10 non-HSV-diseased corneas from seropositive patients, three of whom had evidence for LAT, is intriguing. Four possibilities exist: (1) They may represent false positives. This would appear unlikely, as equivalent results for the presence of HSV DNA were obtained in two centres with the thymidine kinase primers. (2) The original clinical diagnosis may have been incorrect or have masked a herpetic keratitis. (3) A sub-clinical HSV infection occurred. (4) The non-HSV-related corneal disease triggered the seeding of HSV into the cornea. Although further work is needed to answer these possibilities, the question is raised about possible iatrogenic transfer of HSV following penetrating keratoplasty.

What then is the relevance of corneal latency? From a practical point of view the frequency of recurrent disease may be reduced by identifying and avoiding specific triggers that reactivate virus within the cornea. Furthermore virus in the cornea may be more accessible to suppression and eradication than virus in the trigeminal ganglion. This awaits the development of newer methods of treatment directed at the viral genome.

- 1 Southern EM. Detection of specific sequences among DNA fragments separated by gel electrophoresis. *J Mol Biol* 1975; 98: 503–17.
- 2 Shimeld C, Tullio AB, Easty DL, Thomsen J. Isolation of herpes simplex virus from the cornea in chronic stromal keratitis. *Br J Ophthalmol* 1982; 66: 643–7.
- 3 Mullis KB, Faloona FA. Specific synthesis of DNA in vitro via a polymerase-catalyzed chain reaction. *Methods Enzymol* 1987; 155: 335–50.
- 4 Saiki RK, Gelfand DN, Stoffel S, *et al*. Primer-directed enzymatic amplification of DNA with a thermostable DNA polymerase. *Science* 1988; 239: 487–91.
- 5 Paabo S, Gifford JA, Wilson AC. Mitochondrial DNA sequences from a 7000-year-old brain. *Nucleic Acids Res* 1988; 16: 9775–87.
- 6 Sedatati F, Izumi KM, Wagner EK, Stevens JG. Herpes simplex virus type 1 latency-associated transcription plays no role in establishment or maintenance of a latent infection in murine sensory neurons. *J Virol* 1989; 63: 4455–9.

ORIGINAL ARTICLES

Evidence for herpes simplex viral latency in the human cornea

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Abstract

Patients undergoing penetrating keratoplasty for prior herpes simplex keratitis (group A) and corneal disease unrelated to herpes simplex (group B) were investigated to assess whether the cornea is a site for herpes simplex viral latency. All patients were seropositive for herpes simplex viral antibody. Virus was isolated from the tear film postoperatively in one patient and on cocultivation from the cornea of another patient. Herpes simplex viral DNA, however, was detected in the corneas of all patients from group A and half of those from group B by means of the polymerase chain reaction and primers to three well separated regions of the viral genome. Three donor corneas had no evidence of herpes simplex viral DNA. Using RNA polymerase chain reaction, we found evidence of a latency associated transcript and also that of a glycoprotein C coding transcript in two corneas, indicating viral replication. Nine corneas had evidence of a latency associated transcript but no glycoprotein C transcript, which suggests that herpes simplex virus may be maintained in a latent state in the corneas of patients with prior herpes simplex keratitis and in some patients with corneal disease unrelated to the herpes simplex virus.

Herpes simplex virus (HSV) is the commonest infective cause of blindness in many developed countries, where it has a reported incidence of between 5.9 and 20.7 episodes per 100 000 person years.¹⁻³ This appears to be increasing.² Following primary infection with HSV, the virus becomes latent in sensory nerve ganglia. Recurrent herpetic corneal ulceration is thought to result from reactivation of the virus within the trigeminal ganglion and neuronal spread into the cornea.⁴ Most blinding ophthalmic disease is a result of repeated recurrent infections.

Recent studies in humans, however, using an operational definition of latency – namely, the absence of virus in a cell free suspension of fluid derived from the corneal tissue, but the isolation of virus following prolonged organ culture of the excised cornea – have pointed to the cornea as a possible site for harbouring HSV in a latent form.⁵⁻⁸ These studies used an explant culture system without a feeder layer, in which the culture medium containing the corneal disc from patients with herpes simplex keratitis was

regularly sampled and cultured for HSV. Isolations were made between days 4 and 11 after explantation with a frequency of isolation of between 12 and 29.4% of corneas sampled.⁵⁻⁸ In these reports, however, there was no information on the presence of virus in the tear film prior to or following penetrating keratoplasty. This is of importance if one is to exclude the possibility of corneal seeding from a ganglion derived reactivation via the tear film at or before the time of surgery. Furthermore pre-, per-, and postoperative ocular shedding of HSV has important implications for the management of patients undergoing penetrating keratoplasty. Therefore the characterisation of ocular shedding of HSV in the tear film of patients undergoing penetrating keratoplasty was undertaken in the present study. The release of this labile virus within a corneal disc in vitro may be transient, and it may be present in the explant culture medium in a very low concentration.⁷ There is therefore a distinct possibility that virus may not be detected.⁷ The intercellular method of spread of HSV and its suggested origin within the corneal stroma,⁸ impart a time delay between activation of latent virus and/or amplification of a chronic infection within the stroma and entry into the surrounding medium. Furthermore, by analogy with animal studies, the number of cells capable of supporting viral replication may be insufficient, and thus virus may not reach the medium surrounding the cornea.⁹ In an attempt to overcome these problems we used an organ cocultivation technique, thereby improving intercellular contact and increasing the surface area of exposure of the corneal tissue. To improve further the possibility of detecting the presence of virus, half of the available tissue from each cornea was cocultivated in the presence of 5-azacytidine, which has been shown to increase viral reactivation in other models of herpes virus latency.¹⁰

The difficulty encountered by others in demonstrating the presence of HSV in the cornea by conventional culture^{11 12} suggests that if it is present it must be at very low levels. Despite the refinements of the technique here the possibility remained that the virus might still go undetected by cocultivation. The polymerase chain reaction (PCR) can detect as little as a single copy of a gene in 10⁵ cells, and this sensitivity suggested that it might be particularly valuable for the detection of virus in the cornea. We have therefore used primers for the HSV-1 thymidine kinase (TK), glycoprotein C (GC), and major

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capsid protein (MCP) genes to screen DNA extracted from corneas for the presence of viral DNA.

During lytic infection HSV displays a co-ordinated cascade pattern of gene expression characterised by the production of immediately-early, early, and late viral mRNA transcripts. Latent infection, however, is characterised by extremely restricted viral transcription. To date the only viral gene transcripts that have been detected in a latent infection are the latency associated transcripts (LATs).¹³ To establish whether virus detected in the corneas was indeed latent or merely a low grade persistent infection it was necessary to investigate the pattern of viral gene expression. This was done by RNA PCR.

Materials and methods

The study was conducted from June 1989 through June 1990. Informed consent was obtained from and for all patients.

PATIENTS

Patients undergoing penetrating keratoplasty for herpetic and non-herpetic related corneal disease as well as a group of corneal donors were studied.

Group A

Group A comprised 10 patients (five female and five male) who ranged in age from 26 to 72 years. Each patient had a clinically documented history of herpes simplex keratitis, and this had been confirmed by culture in all except patients A2 and A4 (in Table 1). All had received topical acycloguanosine (ACV) for previous episodes of dendritic ulceration. All had had at least one previous episode of disciform keratitis, which had been treated with a combination of topical prednisolone and ACV. Patient A5 had had three previous corneal grafts, each failing because of recurrent herpes simplex keratitis.

All patients had been free from recurrence and without therapy for six to 18 months prior to surgery except for patient A6, who developed a descemetocoele requiring acycloguanosine and urgent penetrating keratoplasty. All had a history of recurrent herpes labialis (HSV-L) (three to six episodes per year), and patients A1 and A3 had had nasal herpes (HSV-N) ipsilateral to the affected eye.

Group B

Group B comprised 10 patients (five females and five males) who ranged in age from 27 to 76 years. All had non-HSV related corneal opacification and had no history of clinically documented HSK. Patients B3, B5, and B8 had had previous cataract surgery and had developed a bullous keratopathy approximately one to three years before surgery. Patients B1 and B2 had evidence of previous bilateral interstitial keratitis characteristic of syphilis. Patients B1 and B3 also had a history of herpes zoster ophthalmicus ipsilateral to the affected eye. Patients B4, B6, B7, B9, and B10 had keratoconus. All patients apart from B8

and B10 had a history of recurrent HSV-L (1–8 episodes per year).

Postoperatively patients were placed on betamethasone 0.1% eyedrops, which in group A were replaced at six weeks by prednisolone 0.05% eyedrops.

Group C

Group C comprised three corneas from donor patients none of whom had a history of corneal disease. They were not suitable for transplantation because of systemic disease.

TEAR FILM SPECIMENS

Patients had specimens collected from both eyes three times a week for two to three weeks prior to surgery, three times a week for four weeks after surgery, and then twice weekly for eight weeks. The last preoperative specimen was collected 30 minutes prior to surgery.

The precorneal tear film was collected by rotation of a swab along the lower fornix to the medial canthus, where it was held to absorb tears for 10 seconds. Care was taken to avoid swabbing the corneal epithelium. Swabs were immediately placed in a sterile transport medium pack (Virocult, UK) and kept on ice prior to inoculation.

All patients had a detailed ocular examination on each visit. Episodes of HSV-L, HSV-N were recorded and the lesions swabbed.

VIRUS ISOLATION FROM TEAR FILM SPECIMENS

Each specimen was assayed for virus in duplicate on confluent Vero cells as previously described.¹⁴ Cultures showing cytopathic effects were maintained until complete cell death and the virus harvested for typing by immunofluorescence with monoclonal antibody (Syva MicroTrak, USA).

ORGAN COCULTIVATION

On removal from the patient one half of the corneal disc was snap frozen in liquid nitrogen, the other transported to the laboratory (10–15 minutes) in 5 ml of growth medium with 20% fetal calf serum (FCS). After microdissection into about 0.5–1 mm pieces, the tissue was resuspended in the growth medium and divided in half. Each half was diluted with growth medium (20% FCS) to a volume of 15 ml, but one half also contained a final concentration of 50 μ M 5-azacytidine. Aliquots (1 ml) of this suspension were placed in tubes of confluent Vero cells. After three days the medium in tubes containing azacytidine was replaced with growth medium (20% FCS). All cultures were fed weekly with GM (20% FCS) and examined daily after day three for viral CPE.

The rims of the 20 donor corneas were also screened for virus by the same procedure. These were not subjected to PCR.

SERUM ANTIBODY

Serum was collected at surgery or within six

weeks postoperatively and assayed for HSV antibody by a complement fixation test.

VERO CELL SENSITIVITY

In order to demonstrate that the sensitivity to HSV-1 infection did not decrease with cell age, tubes containing confluent vero cells were prepared 3 days, 1 week, 2 weeks, and 3 weeks prior to infection. The cells had been re-fed weekly (except for the three-day-old cells) with growth medium (20% FCS). Tubes were inoculated in triplicate with HSV-1 (strain HFEM), 50, 100, and 150 plaque-forming units (PFU) and fed with growth medium (20% FCS). Plaques were counted on day 3 after infection and the results analysed by an F test to test for departure from constancy.

EXTRACTION OF NUCLEIC ACIDS

The hemicorneal disc was cut into small fragments with a separate sterile set of instruments for each specimen and digested at 37°C in 0.5 ml of Hirt buffer (0.01 M Tris pH 8, 0.01 M edetic acid (EDTA), 2% sodium dodecyl sulphate (SDS) containing 0.8 g/l proteinase K (BCL) before two rounds of extraction with 50:50:: phenol:chloroform (nucleic acid grade phenol (Gibco/BRL), saturated with sterile analaR (BDH) water). Nucleic acids were precipitated and redissolved in 50 to 100 µl sterile analaR (BDH) water. Nucleic acid content was determined by electrophoresis and spectrophotometry. Dilutions were made so that 5 µl of nucleic acid solution contained 100–200 ng of DNA. Control DNA from fetal kidney, from the bone marrow of a neuroblastoma patient (negative), and positive control DNA and RNA from Vero cells acutely infected with HSV-1, were prepared by ultracentrifugation through caesium trifluoroacetate gradients.

THE PCR PRIMERS

Samples of nucleic acid from the corneas of patients A1–A7, B1–B5, and C1 and the control DNA, were subjected to PCR by means of primers for the hypoxanthine-guanine phosphoribosyl transferase (HPRT) gene, present in the genome of all human cells,¹⁵ to confirm that the DNA was relatively intact and free from any inhibitors of the PCR.¹⁶ The primers have the sequences

5'-CTTGCTGGTGAAAAGGACCC-3'

5'-GTCAAGGGCATATCCTACAA-3'

and amplify a fragment of 267 base pairs (bp) from DNA. Since the primers span an intron in the gene, the amplification product from RNA is only 97 bp. The primers used to detect the presence of HSV-1 DNA or RNA were: (a) those described previously for the HSV-1 thymidine kinase (TK) gene,¹⁷ which amplify a fragment of 110 bp, (b) those for the glycoprotein C (GC) gene

5'-GTTACACCACAGTCTCTACCG-3'

5'-ATTGCGTCGCGAGAACGTCA-3'

which amplify a fragment of 115 bp, (c) those for the major capsid protein (MCP) gene

5'-GGATGGTATGGTCCAGATGC-3'

5'-AATCTGGTGGCCAACACGGT-3'

which amplify a fragment of 244 bp, and (d) those described previously for the HSV-1 latency associated transcript (LAT),¹⁸ which amplify a fragment of 195 bp.

THE DNA PCR

This was initially performed independently in two different centres (Bristol and Liverpool) on corneas A1–A7, B1–B5, and C1, with the TK primers. All subsequent reactions were in the Liverpool centre. The method was based on that described by Saiki *et al.*¹⁹ In the Bristol Centre the 50 µl reaction mixture contained 10 mM Tris pH 8.3, 50 mM potassium chloride, 1.5 mM magnesium chloride, 33 µM each of dATP, dCTP, dGTP, and dTTP, and was 400 nM with respect to each 20 base primer. In all reactions 5 µl of total nucleic acid mixture and 2.5 units of Taq DNA polymerase (Perkin Elmer) were used. In the Liverpool centre a GeneAmp DNA amplification kit (AmpliAmp, Perkin Elmer) was used. (For the MCP primers the magnesium chloride was 5 mM.) Automatic thermal cyclers (Perkin Elmer: Bristol, and Hybaid: Liverpool) were used.

Reactions began with a 3-minute denaturation at 94°C followed by 40 cycles consisting of denaturation for 1 minute at 94°C annealing at 50°C for 1 minute, and primer extension at 72°C for 1 minute. At the Liverpool centre subsequent reactions were modified, so that after a 3-minute denaturation there were 40 cycles consisting of 40 seconds at 94°C, 15 seconds at 55°C, (50°C for LAT and HPRT), and 20 seconds (30 seconds for MCP) at 72°C, followed by 5 cycles: 40 seconds at 94°C, 30 seconds at 55°C and 40 seconds at 72°C. Samples were confirmed as negative only after a further 20 cycles of amplification. In all experiments both positive and negative control DNAs and a no-DNA control were included. Products were analysed on 12% or 8% polyacrylamide or on 0.8% agarose gels.

RNA PCR

Prior to RNA PCR, nucleic acid samples were digested with RNase-free DNase (Boehringer Mannheim). The RNA recovered was redissolved in 25 µl analaR water and 5 µl used for each reaction. The mRNA complementary PCR primer was annealed to the template RNA in a 20 µl reaction mix (10 mM Tris-HCL pH 8.3, 50 mM KCL, 5 mM MgCl₂, 1 mM each dNTP, 1 µM (0.25 µM LAT) primer, 20 U RNase inhibitor (Boehringer Mannheim) at 45°C for 15 minutes. Reverse transcription by 20 U M-MLV reverse transcriptase (Gibco BRL) followed at 37°C for 60 minutes. After heating to 94°C for 10 minutes, reaction mixtures were prepared for PCR by the addition of 10× PCR buffer (Perkin-Elmer), 400 nM antisense primer (100 nM for LAT primer), Taq polymerase and water to a volume of 50 µl. Each sample was subjected to PCR using HPRT primers (which amplify different size fragments from DNA and RNA) to confirm the presence of RNA and to demonstrate the absence of contaminating DNA. Samples were assayed for expression of LAT and GC. The absence of contaminating DNA was also tested

Table 1 Detection of HSV DNA, RNA, and virus from the cornea and tear film of patients with (group A) and without (groups B and C) prior herpes simplex keratitis

Patient	Tear culture*		Corneal Culture*	DNA PCR			CFT†	RNA GC	PCR LAT
	Pre-op	Post-op		TK	GC	MCP			
A1	0	0	0	+	+	+	160	-	+
A2	0	3+	0	+	+	+	80	+	+
A3	0	0	0	+	+	+	160	-	+
A4	0	0	0	+	+	+	40	-	+
A5	0	0	+	+	+	+	80	+	+
A6	0	0	0	+	+	+	80	NI	NI
A7	0	0	0	+	+	+	40	NI	NI
A8	0	0	0	+	+	+	80	-	+
A9	0	0	0	+	+	+	80	-	+
A10	0	0	0	+	+	+	40	-	+
B1	0	0	0	+	+	+	160	-	+
B2	0	0	0	+	+	+	40	-	+
B3	0	0	0	+	+	+	80	-	+
B4	0	0	0	+	+	+	160	-	-
B5	0	0	0	+	+	+	10	-	-
B6	0	0	0	-	-	-	10	-	-
B7	0	0	0	-	-	-	160	-	-
B8	0	0	0	-	-	-	40	-	-
B9	0	0	0	-	-	-	10	-	-
B10	0	0	0	-	-	-	80	-	-
C1			0	-	-	-	<4	-	-
C2			0	-	-	-	40	-	-
C3			0	-	-	-	40	-	-

*Number of isolations. †Complement fixation test; reciprocal of dilution. +=Amplification product present. -=Amplification product absent. NI=not identified as DNA present.

for, by using the GC primers in an RNA PCR without reverse transcription and by using the antisense primer for reverse transcription. RNA from corneas (PCR negative for HSV DNA) was used as negative control.

CONFIRMATION OF PCR PRODUCT IDENTITY

The amplified DNA fragments of the expected size were electroeluted (Biotrap, BT 1000, Schleicher and Schuell, FRG) and their identity confirmed by restriction endonuclease enzyme digestion. With Sma I (TK), Apa I (MCP), Ksp I (GC), Hae III (LAT), and Ava II (HPRT) (Boehringer Mannheim), the following would be generated: 73 bp and 37 bp (TK), 186 and 58 bp (MCP), 59 and 56 bp (GC), 77 bp, 33 bp and 85 bp (LAT), and 82 and 15 bp (HPRT RNA) respectively. Further confirmation of the 110 bp (TK) amplification product was obtained by hybridisation using a 40 base oligonucleotide of the sequence 5'GAGATGGGGGAGGCTAAC-TGAAACACGGAAGGAGACAATA-3'. The TK amplification products and controls were denatured and 5 µl of each sample including positive (HSV-1) and negative (negative PCR reaction) controls spotted on to a nylon membrane (Hybond-N+, Amersham). Blots were ultraviolet fixed and prehybridised at 55°C for 1 h in 5×SSPE (0.9 M sodium chloride, 0.05 M sodium phosphate, and 0.005 M edetic acid), 0.5% (w/v) sodium dodecyl sulphate 0.016% (w/v) denatured salmon sperm, and 0.1% (w/v) each of bovine serum albumin, ficoll (Sigma), and polyvinylpyrrolidone (BDH). Hybridisation was over night at 55°C with (α³²P) dCTP (Amersham) labelled probe.²⁰ Blots were washed twice at 20°C in 2×SSPE, 0.1% (w/v) sodium dodecyl sulphate for 2 minutes, followed by two washes in pre-warmed 1×SSPE, 0.1% (w/v) sodium dodecyl sulphate at 55°C for 5 minutes and autoradiographed. Blots were stripped by washing in 0.5% (w/v) sodium dodecyl sulphate at 95°C for 10 minutes and rehybridised with an (α³²P) dCTP

HLA probe at 68°C. Washing was in 2×SSPE, 0.1% (w/v) sodium dodecyl sulphate for 5 minutes at 20°C followed by two washes in 0.1×SSPE, 0.1% (w/v) sodium dodecyl sulphate at 68°C for 10 minutes.

Results

VERO CELL RESPONSES

The average numbers of plaques produced on Vero cells monolayers aged 22, 14, 7, and 3 days at inoculation were not significantly different for each of the three inocula respectively (F test, $p>0.1$). Thus the sensitivity of Vero cells to infection with HSV did not vary with the age of the cells within the three-week period used in the cocultivation experiments.

PREOPERATIVE PERIOD

In total, 82 and 72 specimens were collected from groups A and B respectively. There was no HSV-1 isolations (Table 1). Patients B1 and B4 had episodes of HSV-L one and two weeks prior to surgery respectively. There were no episodes of HSV-N.

POSTOPERATIVE PERIOD

Two hundred and forty-seven and 220 tear film specimens were collected from groups A and B (Table 1). There were three isolations (all HSV-1). They were made consecutively and were from the affected eye of patient A2. The first isolation was on day 18 after surgery, three days after commencement of topical timolol (0.25%) for raised intraocular pressure. On day 24 an epithelial ulcer developed and topical ACV was started, with resolution of the ulcer over the next five days.

There were no isolations from the donor corneas, C1, C2, and C3. Three patients in group A (3, 4, 7) and three in group B (2, 4, 5) had sutures removed and or replaced. Patients A3 and A1 had one and two episodes of HSV-N (HSV-1) ipsilateral to the affected eye, at four, five, and nine weeks after surgery. There were four episodes of HSV-L (HSV-1).

ORGAN COCULTIVATION

There were two isolations (both HSV-1) on day 4 of tissue incubation. Both were from the corneal disc of patient A5. The isolations were in tubes that did not contain 5-azacytidine. No other isolations were made from either the corneas or the rims of donor corneal tissue.

POLYMERASE CHAIN REACTION

A positive result was taken as a visible band of the predicted molecular weight for the particular set of primers.

DNA PCR

All corneas from those patients in group A (10) as well as five (B1-B5) out of 10 in group B produced a positive result to all three (TK, GC,

and MCP primers (Table 1). Corneas C1, C2, C3, and B6-B10 produced a negative result. Both negative and positive results were reproducible in further PCRs (up to three times), and replicate assays in Bristol and Liverpool produced identical results.

RNA PCR

Using the HPRT primers we showed that all but two corneas contained mRNA and no DNA. Corneas from patients A6 and A7 showed evidence of residual DNA by this method, by omission of the reverse transcriptase step and by use of the antisense primer, and were thus excluded from further analysis. All eight of the remaining corneas from group A, as well as three from group B (B1-B3) showed evidence of the presence of a LAT. Among these corneas evidence of GC mRNA was found only in patients A2 and A5 (Table 1).

PRODUCT DIGESTION AND HYBRIDISATION

All amplification products were cleaved as predicted by the relevant restriction enzyme, thus confirming their identities. Similarly, all TK amplification products from positive samples hybridised to the internal oligonucleotide probe, whereas the negative control samples did not. In addition none of the positive samples hybridised to the HLA probe, thus confirming their specificity.

SERUM ANTIBODY

All patients were HSV seropositive apart from C1 (titre less than 1/4) (Table 1). There was no significant difference in antibody levels between groups A and B (*t* test, $p > 0.1$), nor between patients in group B who had evidence of HSV DNA in their corneas and those who did not (*t* test, $p > 0.1$).

Discussion

The absence of preoperative shedding of HSV is not unexpected¹⁴ and makes it unlikely that virus was seeded into the cornea at or recently before surgery. The onset of early postoperative shedding on day 18 followed by the development of recurrent herpes simplex keratitis on day 24 (patient A2), has not been reported previously. Early recurrence, that is within 12 months, is usually associated with an event such as rejection or suture removal²¹ and is epithelial in nature in greater than 72% of cases.^{21,22}

Although timolol has been used to induce shedding and recurrent herpes simplex keratitis in rabbits²³ and more recently in a non-human primate,²⁴ there are at present no studies in humans. Whether timolol induced shedding and recurrence in this patient (A2) is unknown. Acycloguanosine has been found to reduce herpes simplex keratitis recurrence in rabbit models of penetrating keratoplasty.²⁵ Although prophylactic antiviral cover after suture removal or replacement has been recommended,^{21,22} the absence of shedding and/or recurrence in four patients in group A who had sutures removed or

replaced raises questions in this regard. The need for prophylactic antiviral therapy and regular tear film sampling in patients following penetrating keratoplasty for herpes simplex keratitis is debatable and needs further investigation.

The isolation of HSV from one of the corneas of those patients with prior herpes simplex keratitis (one out of 10) is in accord with some previous reports,⁵⁻⁸ which are in turn at variance with others in which no isolations were reported.^{11,12}

The infrequency of an isolation in this study may reflect the use of acycloguanosine during active herpes simplex keratitis and the long period of quiescence (six to 18 months) prior to surgery. The absence of an isolation in the 5-azacytidine treated cultures may be due in part to its effect on viral replication. This could be investigated by reducing the concentration of 5-azacytidine to 15 μM , at which concentration its effect on replication is markedly reduced.¹⁰

We have demonstrated that HSV-1 DNA sequences are present more frequently in diseased human corneas than previously thought. Patients with previous herpes simplex keratitis are highly likely to have HSV-1 DNA in their corneas. This is consistent with previous reports which have demonstrated HSV viral antigens in corneal discs taken from patients with previous herpes simplex keratitis.^{11,12,26} Furthermore we have shown that patients with no documented history of herpes simplex keratitis, who have non-HSV related corneal disease and who are HSV seropositive, may have HSV DNA within their corneas. We used primers that amplify three segments that are widely separated on the HSV-1 genome. In each case when DNA products were found all three segments were present. Thus it is reasonable to assume that the whole of the HSV-1 genome was present. That HSV-1 DNA was found in herpes simplex keratitis corneas implies that its presence is not always associated with typical clinically recognisable disease. Indirect support for this occurrence may be adduced from the finding that secretory anti-HSV antibody can be found in the tear film of individuals who do not have serum anti-HSV antibody, and raises the possibility that the eye may be a primary portal of entry for HSV,²⁷ and that spread beyond the eye need not necessarily occur.

The presence of HSV-1 DNA in these corneas could be explained by the presence of replicating virus in a low grade persistent infection, by viral DNA remaining from previous infection, or by latent virus. The first possibility appears unlikely, since infectious virus was isolated by cocultivation from only one of the 15 corneas containing HSV DNA. In an attempt to demonstrate that the DNA was from latent virus it was necessary to investigate the pattern of viral gene transcription, which so far appears to be confined to LATs during latent infection. Because of the limited amount RNA available it was not possible to study the expression of a wide range of HSV genes, and investigations were confined to the LAT and GC genes. Of the genes for which primers were available, GC was selected, since it is a late or δ gene, and so its expression is likely to

be a marker for the production of infectious virus.

Two of the corneas were found to contain GC transcripts, and one of these was the cornea from which virus was isolated by cocultivation. Although no virus was isolated from the other, the viral DNA detected in both was assumed to be present as actively replicating virus. A further two corneas apparently contained GC mRNA, but the signal was probably due to a minute amount of remaining DNA. The samples still gave a positive result for GC, when reverse transcription was omitted or the antisense GC primer used, and RNA PCR with the HPRT primers produced bands of expected size for amplification from both DNA and RNA templates.

In nine of the 11 remaining corneas which did not contain evidence of GC mRNA we could amplify a fragment of LAT. The presence of LAT transcripts in the absence of GC mRNA suggests that viral gene transcription is limited in these corneas, and, within the limits of this study, follows the pattern of a neuronal type of latent infection. Our results must be further evidence for the possibility of corneal latency, though they are not unequivocal proof. Further investigation of the gene expression is necessary, particularly of other genes previously postulated to have a role in the establishment and maintenance of latency, such as infected cell protein O (ICPO), TK, and ribonucleotide reductase. Truly latent virus should be capable of reactivation, which we were unable to detect under the conditions described. Different cocultivation conditions may promote reactivation and improve detection of the low levels of virus likely to be involved. Nevertheless, it appears that in some patients HSV may be maintained in a latent state in the cornea, and this is not always related to prior herpes simplex keratitis. The implication of these findings to our understanding of the pathogenesis of herpes simplex keratitis are not yet clear.

- 1 Dawson CR, Togni B. Herpes simplex eye infections: clinical manifestation, pathogenesis and management. *Surv Ophthalmol* 1976; 21: 121-35.
- 2 Liesegang TJ, Meiton J III, Daly PJ, Ilstrup DM. Epidemiology of ocular herpes simplex: incidence in Rochester, Minn, 1950 through 1982. *Arch Ophthalmol* 1989; 107: 1155-9.
- 3 Norn MS. Dendritic (herpetic) keratitis, I: incidence - seasonal variations - recurrence rates - visual impairment - therapy. *Arch Ophthalmol (Kbh)* 1970; 48: 91-107.
- 4 Nesburn A, Cook M, Stevens JG. Latent herpes simplex infection from trigeminal ganglia of rabbits with recurrent eye infections. *Arch Ophthalmol* 1972; 88: 412-7.
- 5 Shimeld C, Tullo AB, Easty DL, Thomsit J. Isolation of herpes simplex virus from the cornea in chronic stromal keratitis. *Br J Ophthalmol* 1982; 66: 643-7.
- 6 Tullo AB, Easty DL, Shimeld C, Stirling PE, Darville JM. Isolation of herpes simplex virus from corneal discs of patients with chronic stromal keratitis. *Trans Ophthalmol Soc UK* 1985; 104: 159-64.
- 7 Coupes D, Klapper PE, Cleator GM, Baily AS, Tullo AB. Herpes virus simplex in chronic human stromal keratitis. *Curr Eye Res* 1986; 5: 735-8.
- 8 Easty DL, Shimeld C, Cloue CMP, Menage M. Herpes simplex virus isolation in chronic stromal keratitis: human and laboratory studies. *Curr Eye Res* 1987; 6: 69-74.
- 9 Abbigari SZ, Stulting RD. Recovery of herpes simplex virus from ocular tissues of latently infected inbred mice. *Invest Ophthalmol Vis Sci* 1988; 29: 239-43.
- 10 Mossman SP, Leib DA, McCarthy K, Hart CA. The effects of 5-azacytidine, 12-O-tetradecanoylphorbol 13-acetate and sodium n-butyrate on reactivation of alphaherpesvirus saimiri from explant cultures of latently infected rabbit dorsal root ganglia. *J Gen Virol* 1989; 70: 2507-12.
- 11 Dawson C, Togni B, Moore TE. Structural changes in chronic herpetic keratitis. *Arch Ophthalmol* 1968; 79: 740-7.
- 12 Metcalf JF, Kaufman HE. Herpetic stromal keratitis - evidence for cell-mediated immunopathogenesis. *Am J Ophthalmol* 1976; 82: 827-34.
- 13 Wagner EK, Devi-Rao G, Feldman LT, et al. Physical characterization of the herpes simplex virus latency-associated transcript in neurons. *J Virol* 1988; 62: 1194-202.
- 14 Kaye SB, Madan N, Dowd T, Hart C, McCarthy K, Patterson A. Ocular shedding of herpes simplex virus. *Br J Ophthalmol* 1990; 74: 114-6.
- 15 Caskey CT, Kruh GD. The HPRT locus. *Cell* 1979; 16: 1-9.
- 16 Maitland NJ, Cox MF, Lynas C, Prime S, Crane I, Scully C. Nucleic acid probes in the study of viral disease. *J Oral Pathol* 1987; 16: 199-211.
- 17 Lynas C, Cook SD, Laycock KA, Bradfield JWB, Maitland NJ. Detection of latent virus mRNA in tissues using the polymerase chain reaction. *J Pathol* 1989; 157: 285-9.
- 18 Lynas C, Laycock KA, Cook SD, Hill TJ, Blyth WA, Maitland NJ. Detection of herpes simplex virus type 1 gene expression in latently and productively infected mouse ganglion using the polymerase chain reaction. *J Gen Virol* 1989; 70: 2345-55.
- 19 Saiki RK, Gelfand DH, Stoffel S, et al. Primer-directed enzymatic amplification of DNA with a thermostable DNA polymerase. *Science* 1988; 239: 487-91.
- 20 Feinberg AP, Vogelstein B. A Technique for radiolabelling DNA restriction endonuclease fragments to high specific activity (addendum). *Anal Biochem* 1984; 137: 266-7.
- 21 Ficker LA, Kirkness CM, Rice NSC, McG Steele AD. Longterm prognosis for corneal grafting in herpes simplex keratitis. *Eye* 1988; 2: 400-8.
- 22 Fine M, Cignetti FE. Penetrating keratoplasty in herpes simplex keratitis. *Arch Ophthalmol* 1977; 95: 613-6.
- 23 Haruta Y, Rootman DS, Hill JM. Recurrent HSV-1 corneal epithelial lesions induced by timolol iontophoresis in latently infected rabbits. *Invest Ophthalmol Vis Sci* 1988; 29: 387.
- 24 Rootman DS, Haruta Y, Hill JM. Reactivation of HSV-1 in primates by transcorneal iontophoresis of adrenergic agents. *Invest Ophthalmol Vis Sci* 1990; 31: 597-600.
- 25 Beyer CF, Arens MQ, Hill GA, Rose BT, Beyer LR, Schanzlin DJ. Oral acyclovir reduces the incidence of recurrent herpes simplex keratitis in rabbits after penetrating keratoplasty. *Arch Ophthalmol* 1989; 107: 1200-5.
- 26 Meyers-Elliott RH, Pettit TH, Maxwell WA. Viral antigens in the immune ring of herpes simplex stromal keratitis. *Arch Ophthalmol* 1980; 98: 897-904.
- 27 Coyle PK, Sibony PA. Viral antibodies in normal tears. *Invest Ophthalmol Vis Sci* 1988; 29: 1552-8.



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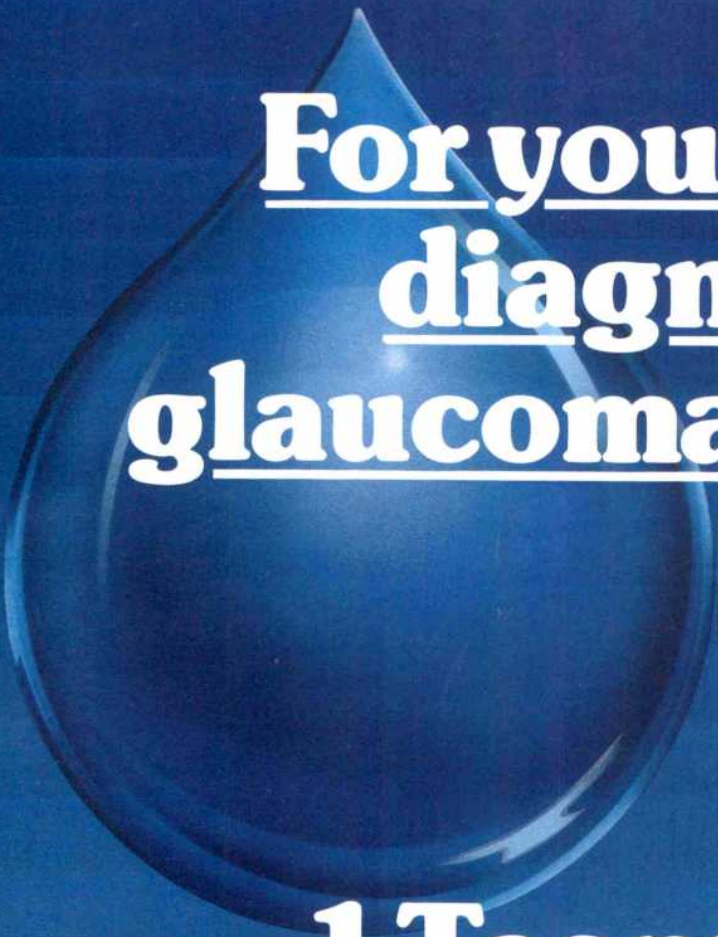
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References

1. Maclure, G.M. et al. 3rd Congress of European Glaucoma Society, 1988.
2. Kitazawa, Y. et al. Acta XXIV International Congress of Ophthalmology, 1983. P. Henkind (Ed), Lippincott, Philadelphia.
3. Hugues, F.C. et al. J. Fr. Ophthalmol. 1987; **10**, 8/9, 485-490.
4. Negishi, C. Acta Soc. Ophthalmol. Jpn. 1982; **85**, 57-66.
5. Scoville, B. et al. American Journal of Ophthalmology, 1988; **105**, No.2, 150-154.

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Diagnosis and management of systemic Wegener's granulomatosis presenting with anterior ocular inflammatory disease

Stephen J Charles, Paul A R Meyer, Peter G Watson

Abstract

The ocular and systemic features of 10 patients whose Wegener's granulomatosis presented with corneoscleral inflammatory disease are described. Marginal corneal infiltrates were seen in all patients with anterior scleritis and were a valuable sign of disease activity. Nine out of 10 patients had symptoms of systemic vasculitis on presentation; seven had renal impairment; three had chest x-ray abnormalities. Autoantibodies against neutrophil cytoplasmic determinants (ANCA) were present in all cases. In seven patients the scleritis responded well to pulsed immunosuppressive therapy followed by long term oral steroids and cyclophosphamide. Oral steroid therapy alone failed to control severe disease. Corneoscleral disease was not a cause of visual loss. It is important to realise that inflammatory corneoscleral disease may be the presenting feature of a severe systemic vasculitis.

Wegener's granulomatosis (WG) is a multifocal necrotising vasculitis which most commonly affects the lungs, upper respiratory tract, and kidneys.^{1,2} In consequence patients may present with haemoptysis from cavitating areas of pulmonary consolidation, sinusitis and serous otitis media, or renal failure resulting from chronic glomerulonephritis. Untreated, the disease used to be rapidly fatal, usually as a result of renal failure.³

The eye is involved in between 28%⁴ and 58%² of cases, and patients often present with the ocular manifestations. There may be orbital

invasion by paranasal sinus granulomata,⁵ producing painful proptosis with ophthalmoplegia and optic nerve compression, or a focal vasculitis^{6,7} causing scleritis and peripheral corneal disease. In the past ocular involvement caused severe visual loss regardless of treatment.⁸

The affected tissues show a necrotising vasculitis with granuloma formation,¹ and leucocyte fragments have been demonstrated in the lumina of the inflamed vessels by electron microscopy.⁹ The characterisation of the disease has recently been facilitated by the detection of autoantibodies against neutrophil cytoplasmic determinants (ANCA) in patients with systemic vasculitis, especially WG and microvascular polyarteritis (MPA).¹⁰⁻¹² Two types of autoantibody have recently been identified: c-ANCA active against a 29 kD protease¹³ and p-ANCA directed against myeloperoxidase.¹⁴ The former appears to be specific for WG, while p-ANCA has been found in other forms of vasculitis such as MPA.¹⁵

The treatment of choice in WG has been a combination of systemic corticosteroids and a lymphocytotoxic agent, of which cyclophosphamide is the most effective.^{2,16} Pulsed intravenous corticosteroids and cyclophosphamide,¹⁷ and plasma exchange,¹⁸ have also been used to control the acute phase of the disease.

In this study we describe the ocular and systemic features of a series of patients whose WG presented with anterior ocular disease. We also consider the consequences for ocular morbidity when treatment is directed against the underlying systemic disease.

Table 1 Results of investigations at presentation with eye disease

Investigation	Patient	Scleritis without necrosis			Scleritis with necrosis						
		1	2	3	4	5	6	7	8	9	10
CKR changes		—	—	—	+	—	—	+	+	—	—
Sinus XR changes		+	—	+	—	+	+	+	+	+	—
Hb (g/dl)		13.8	12.1	10.3	11.6	13.2	12.4	9.4	11.3	8.0	15.3
WBC ($\times 10^9/l$)		5.9	10.8	13.5	14.8	7.9	12.0	11.8	11.2	10.8	8.9
Platelets ($\times 10^9/l$)		432	534	847	495	263	386	832	814	651	243
ESR (mm/h)		19*	123	129	83	32*	114	121	89	>140	35
CRP (mg/l)		ND	123	192	109	9*	97	138	57	284	16
Immune complexes (normal <30 µg/l)		<30	10	28	4	ND	40	72	33	ND	ND
Complement		N	Raised C3C4	N	N	N	Raised C4	Raised C3C4	N	N	ND
Raised immunoglobulins		N	IgA	IgG	N	N	IgG	IgG	IgA IgG	ND	N
Raised ANCA titre		†	+	+	+	‡	+	+	+	+	‡
Creatinine clearance ml/min		ND	84.5	62.5	98.8	71.3	53.1	41.9	20.5	3.84	126
Biopsy: Renal		+	+	+	+	+	+	+	+	+	+
Nasal											
Other											

*On steroid therapy. ND=not done. N=normal. †ANCA testing not yet available when patient 1 initially presented, but ANCA was elevated when tested later. ‡Became raised.

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Patients and methods

Between 1986 and 1989 ten patients (six females and four males) were seen in Addenbrooke's Hospital with scleritis complicating WG. All presented with scleritis, with or without corneal guttering, and had features compatible with WG in nasal mucosal or renal biopsies, together with increased ANCA.

Each patient underwent full medical examination, and their investigations are listed in Table 1. The ANCA were measured by a solid phase radioimmunoassay (RIA); test sera were quantified as a percentage of the binding of a reference strong positive serum (normal range <16%). Indirect immunofluorescence (IIF) was performed to distinguish granular cytoplasmic staining (c-ANCA) from a perinuclear staining pattern (p-ANCA).

Clinical findings

The patients were divided into two groups according to the absence or presence of scleral necrosis. The age at onset of disease ranged from 38–65 years (mean 56.6 years).

SCLERITIS WITHOUT SCLERAL NECROSIS

Systemic disease

The first patient in this group appeared to suffer from scleritis alone, but developed renal failure four years later. Two other patients suffered from arthralgia at the time of their presentation; one also complained of epistaxis. Both were found to have renal disease. None had any evidence of lung disease.

Renal biopsies in two patients demonstrated respectively mesangioproliferative glomerulonephritis and acute glomerular necrosis. In the third patient nasal mucosal biopsy showed necrotising vasculitis affecting small arteries and venules, with granuloma formation. The ANCA titre (RIA) was raised in all three cases, and IIF confirmed granular cytoplasmic staining in two cases.

Ocular disease

All patients had anterior scleritis (Fig 1), in which different sectors became involved during the course of the disease; a mild anterior uveitis was also present in one.

Limbal subepithelial infiltrates were seen in two cases, but thinning was not present. In one case areas of corneal epithelial disturbance were seen.

Case history: patient 2: scleritis, limbal ischaemia and proteinuria

A 51-year-old woman with a two-year history of recurrent episcleritis presented with right anterior scleritis and marginal corneal subepithelial infiltrates. She also complained of a painful swollen foot. The erythrocyte sedimentation rate (ESR) was 123 mm/h and despite normal urea and electrolytes there was heavy proteinuria and reduced creatinine clearance. Chest and sinus x-rays were normal. The ANCA

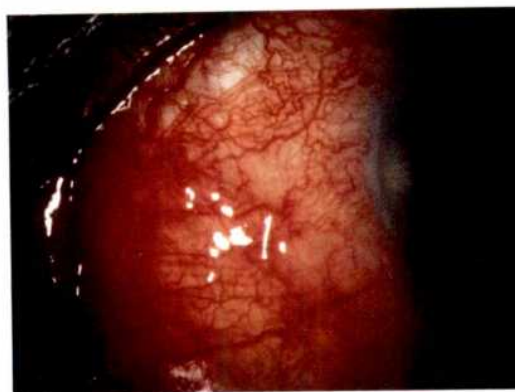


Figure 1 Anterior scleritis without scleral necrosis (patient 3) may be the presenting feature of WG. Scleral oedema is accompanied by episcleral venous congestion.

titre was not raised and the eyes settled without treatment.

Four weeks later the ANCA titre rose (RIA = 44%), and renal biopsy showed mesangial proliferation compatible with, but not diagnostic of, a systemic vasculitis such as WG or MPA. No treatment was instituted.

Four months later she developed bilateral multifocal marginal corneal epithelial defects (Fig 2) and granular subepithelial deposits. Herpetic infection was suspected, but no virus could be isolated, and there was no response to topical antiviral agents. Haemoglobin video imaging showed severe limbal hypoperfusion, and the epithelial defects were therefore attributed to limbal ischaemia. Her systemic vasculitis was controlled by cyclophosphamide and prednisolone, and, after two weeks, perfusion of the limbal arcades had returned to normal and the epithelial defects had disappeared. Leucopenia and alopecia prompted reduction of the cyclophosphamide dose. She has had episodes of arthralgia but is currently controlled on cyclophosphamide (1.5 mg/kg) and prednisolone 10 mg daily.

SCLERITIS WITH SCLERAL NECROSIS

Systemic disease

Seven patients (four males, three females) presented with necrotising scleritis. All had symptoms of systemic disease; arthralgia (3), cough and breathlessness (2), pain over the

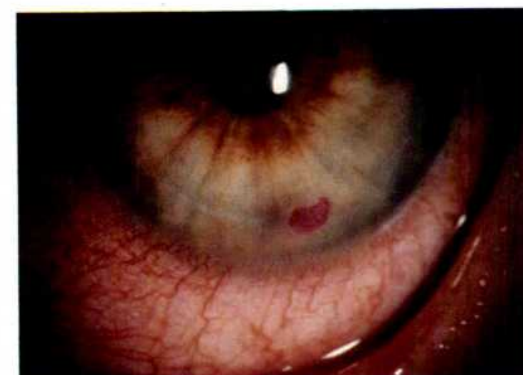


Figure 2 Unusual marginal corneal epithelial defect demonstrated by rose-Bengal stain (patient 2). Haemoglobin videomaging showed hypoperfusion of the adjacent limbal arcades. The lesion was not affected by antiviral therapy but resolved after immunosuppression.

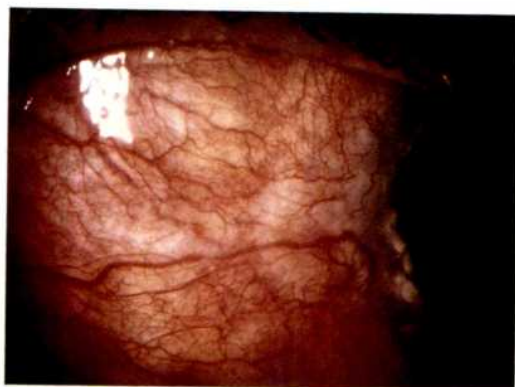


Figure 3 Anterior scleral necrosis with conjunctival cover (Patient 4). Note yellow colour of necrotic sclera and the adjacent marginal corneal infiltrates, which are multifocal, grey and have diffuse edges.



Figure 4 Anterior scleral necrosis with loss of conjunctival cover. The scleral necrosis is confluent with a circumferential corneal melt (patient 8).

maxillary sinuses (6), epistaxis (6), and deafness (3).

Sinus x-rays revealed mucosal thickening or sinus opacification in five patients. Three cases had chest x-ray evidence of pulmonary consolidation, two with cavitation (Fig 6). Creatinine clearance indicated renal impairment in five patients.

Nasal mucosal biopsy provided histological confirmation of vasculitis in six patients and showed granuloma formation in five. Conjunctival biopsy (prior to referral) had shown vasculitis in a further case. The ANCA titre was also raised in all these patients. However, one had a normal titre at presentation, which was raised 18 months later. IIF could be demon-

strated in six cases, and in all of these c-ANCA was confirmed.

Ocular disease

Scleritis. Scleral necrosis appeared to arise at a single focus, which evolved either by enlargement or by the development of satellite lesions (Fig 5A). Superior sclera was involved in four subjects, inferior in one and nasal in three. Ultrasound demonstrated spread to post-equatorial sclera in two patients. Necrotic sclera appeared yellow when viewed with low intensity, diffuse light (Fig 3). The overlying conjunctiva remained intact in two patients (Fig 3) but had become lost in five by the time of presentation (Figs 4, 5A, 7A).

Subconjunctival haemorrhage was present in five patients.

Limbal changes. The scleral necrosis transgressed the limbus in three patients (Fig 4) and evidence of limbal vascular remodelling was found in the remainder.

Corneal infiltrates. Multifocal stromal infiltrates below Bowman's membrane extended centrally from the limbus in every patient (Fig 3). Disease activity was accompanied by enlargement of the infiltrates and loss of definition of their borders. Conversely, during periods of remission they became smaller and more discrete (Fig 7d).

Corneal guttering was present in four patients. Gutters arose only central to areas of scleral necrosis (Fig 5A). Circumferential progression was characterised by stromal oedema at the



Figure 5A Corneal guttering central to areas of scleral necrosis with loss of conjunctival cover (patient 7). Note collagen plug in corneal gutter (arrowed) and necrotic tissue emerging from conjunctival defects.

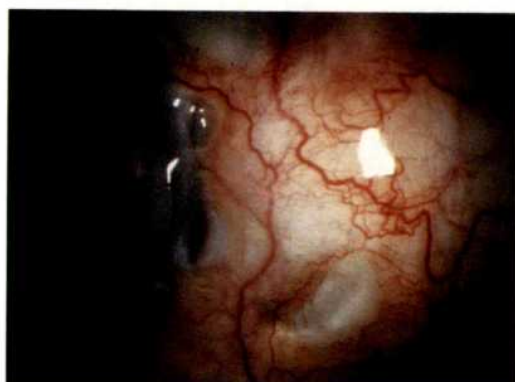


Figure 5B Same patient one week later, after two pulses of intravenous cyclophosphamide and methylprednisolone. The corneal plug from the nasal gutter has been lost, revealing a limbal perforation.

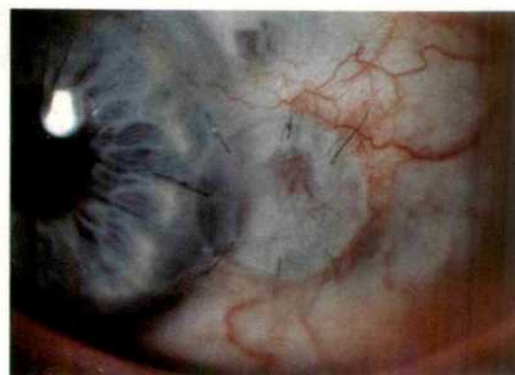


Figure 5C Lamellar corneoscleral graft performed after medical control of disease activity.

leading edge. The central limit of the gutter was shelving in three cases and steep in one. Limbal perforation occurred in one patient (Fig 5B) but anterior chamber depth was maintained, allowing corrective corneoscleral lamellar patch grafting to be delayed until disease activity had been fully controlled (Fig 5C).

Uveitis. A few cells and minimal flare were present in four cases.

Case history: patient four: nodular scleritis with cavitating lung lesions

A 39-year-old woman, with a past history of polyarthralgia, developed left anterior scleritis. This initially responded to high dose oral steroids, but then relapsed accompanied by a cough, a sore throat and malaise. She first attended our unit with visual acuities of 6/5 OD and 6/36 OS, left nodular scleritis with disruption of the adjacent limbal arcade, and superficial marginal stromal corneal infiltrates (Fig 3).

Chest x-ray revealed multiple cavitating areas of pulmonary consolidation (Fig 6), but sinus x-rays were normal. The ESR, c-reactive protein (CRP), and ANCA titre were raised, but renal function was normal. Though ear, nose, and throat examination gave normal findings, nasal mucosal biopsy showed active vasculitis with a giant cell infiltrate, granuloma formation, and necrosis diagnostic of WG.

After three pulses of intravenous methylprednisolone and two of cyclophosphamide her scleral nodule diminished. Despite daily oral prednisolone (20 mg) and cyclophosphamide (1.5 mg/kg), scleritis recurred in a different site one month later. This responded to two further pulses of methylprednisolone and cyclophosphamide. Maintenance cyclophosphamide was increased, but after six months was replaced

by azathioprine. Her scleritis relapsed on the new regimen, now involving postequatorial sclera with severe posterior uveitis. She also developed a pericardial effusion. Cyclophosphamide was restored and the scleritis is now controlled, but visual acuity in the affected eye is reduced to counting fingers (CF) by a macular hole complicating chronic cystoid macular oedema secondary to posterior uveitis.

Case history: patient 8. Scleral necrosis, deafness, pulmonary cavitation, and renal failure

A 64-year-old man presented with a two-month history of arthralgia affecting his knees and elbows, nasal obstruction, and epistaxis, then soreness of both eyes and unilateral deafness. Visual acuities were 6/6 OD and 6/9 OS. There was bilateral superior scleral necrosis, with necrosis of the overlying conjunctiva, widespread pericapillary haemorrhages, and damage to the limbal vascular arcades (Fig 4). Marginal corneal infiltrates were accompanied by early corneal gutter formation and mild anterior uveitis.

The ESR and CRP were raised and there were microscopic haematuria, proteinuria, and reduced creatinine clearance (20.5 ml/min). Chest x-ray showed a cavitating pulmonary lesion, and sinus x-rays showed antral mucosal thickening. The ANCA titre was found to be raised. Nasal mucosal biopsy showed features suggestive of WG and renal biopsy severe necrotising glomerulonephritis. The patient was treated with pulsed intravenous methylprednisolone and cyclophosphamide. Despite an improvement in his scleritis, his creatinine clearance continued to fall and plasma exchange was started. This reduced circulating ANCA and improved renal function. His disease is currently controlled by prednisolone 10 mg and cyclophosphamide 40 mg daily, and both eyes have retained visual acuities of 6/6.

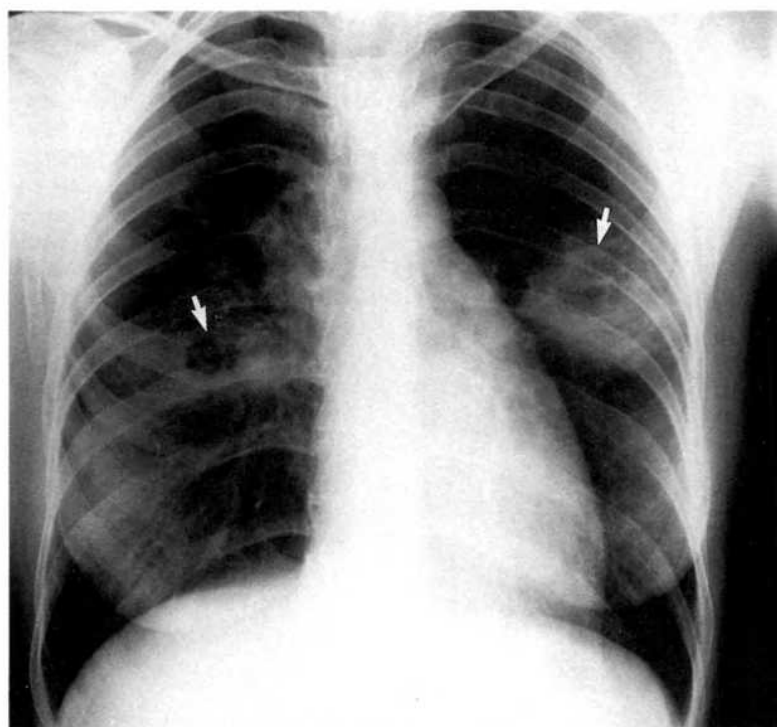


Figure 6 Chest x-ray (patient 4) showing cavitation within areas of pulmonary consolidation (arrowed), typical of WG.

Treatment

All patients were admitted to hospital for investigation and clinical evaluation.

Non-steroidal anti-inflammatory agents had been used prior to admission in six patients but were never successful.

Oral steroids were used in all patients but alone never controlled acute disease. In two patients (without scleral necrosis) control was achieved by additional oral cyclophosphamide.

Pulsed immunosuppressive therapy (intravenous methylprednisolone and cyclophosphamide¹⁹) was used in the seven patients, six with scleral necrosis, who had not responded to oral steroids and in whom scleritis was progressing rapidly. Intravenous injections of methylprednisolone (0.5–1.0 g) were repeated at three-day intervals until the scleritis had subsided: no more than four injections were ever required. Cyclophosphamide (0.5 g) usually accompanied the first two pulses of methylprednisolone. Oral prednisolone (15–20 mg) was started with the first pulse, and cyclophosphamide (2 mg/kg) was added when its intravenous administration ceased. This treatment achieved control of scleritis in all patients in whom it was used.



Figure 7A Necrotising scleral granuloma with loss of conjunctival cover (patient 5).

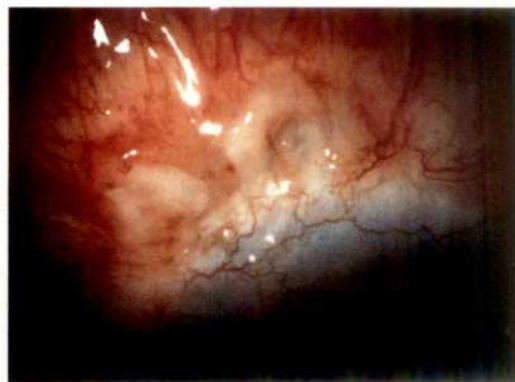


Figure 7C After involution of the granulation tissue, the exposed sclera became covered by a fibrovascular membrane. This contracted, distorting the conjunctival vascular pattern.



Figure 7B The same patient five weeks later, showing excessive granulation tissue which developed during recovery. It was centred on a perforating deep scleral artery.



Figure 7D Corneal stromal infiltrates during remission, demonstrated by retroillumination in the same eye.

Plasma exchange was used in two patients with severe progressive renal disease: one had received pulsed immunosuppressive therapy, which had appeared to control the scleritis but not the renal disease; the other presented in severe renal failure and was also treated with oral cyclophosphamide and prednisolone.

Azathioprine was substituted for cyclophosphamide in one patient in remission, and prompted an immediate relapse.

Surgery was required in one patient. A corneo-scleral patch graft was performed for a limbal perforation after the disease had been controlled medically (Fig 5C).

CLINICAL PROGRESS

In areas of conjunctival necrosis exposed sclera became covered by fibrovascular tissue from adjacent conjunctiva. These neovascular membranes contracted, distorting the surrounding conjunctival vascular pattern (Figs 7A, B, C). Granulation tissue was pronounced in one patient (Fig 7B). It arose in a zone of scleral necrosis, was centred on a perforating deep scleral artery, and later became infarcted.

During remission marginal corneal infiltrates became smaller, better defined, and more refractile in nature but did not disappear completely (Fig 7D).

FOLLOW-UP

Six out of 10 patients required no further pulsed immunosuppressive therapy to control their scleritis (follow-up 11 to 72 months, mean 25

months). One (two cases) or two (two cases) further pulsed treatments were necessary in four patients.

Five patients had relapses of their systemic WG giving rise to acute renal failure (1), progressive renal failure (2), pericardial effusion (1), rashes (1), and arthralgia (3). One patient now requires haemodialysis.

Two out of 10 patients lost visual acuity in one eye after presentation: from 6/36 to counting fingers due to a macular hole secondary to cystoid macular oedema and uveitis in one; and from 6/24 to 5/60 due to retinal vascular occlusion complicating thrombocytosis in the other. Anterior segment changes such as guttering and perforation did not produce visual loss.

Intravenous methylprednisolone and cyclophosphamide were well tolerated apart from transient hyperglycaemia and electrolyte disturbances. Four patients became mildly cushingoid (with weight gain and facial changes), and one developed osteoporosis on prolonged systemic steroids. Alopecia was symptomatic in two patients. Pneumonia associated with cyclophosphamide-induced leucopenia and requiring admission to hospital arose in two patients. One patient suffered from herpes simplex virus pharyngitis. Later, when his WG was inactive, he died of a viral myocarditis. Although he was not severely leucopenic (leucocytes $3.3 \times 10^9/\text{dl}$), this may have been related to his immunosuppression.

Discussion

This paper considers the manner in which WG

may present in an eye clinic, though our cases reflect a bias in this centre towards corneoscleral inflammatory disease. The mildest scleritis was accompanied by critical involvement of other systems, and even when no symptoms were volunteered they could be revealed by careful questioning. The discovery of systemic disease was vitally important to all our patients, and treatment of this, rather than the eye in isolation, reduced ocular morbidity.

The scleral changes with which these patients presented included episcleral vasodilatation and oedema, scleral oedema, and scleral necrosis, which was often accompanied by destruction of the overlying conjunctiva. Although conjunctival necrosis is a dramatic physical sign, the presence of scleral necrosis correlated best with the extent of systemic involvement.

It has been proposed that corneoscleral destructive disease straddling the limbus characterises systemic vasculitis.^{20,21} Every patient with scleral necrosis did have multifocal, peripheral corneal infiltrates beneath Bowman's membrane, showing the vulnerability of the limbal arcades in this condition. This is to be the subject of a further paper. Corneal guttering arose less frequently, and always adjacent to necrotic sclera.

Although scleritis was the presenting symptom in all our patients, it was not responsible for visual loss. When this occurred, it resulted from cystoid macular oedema complicating uveitis in one case and retinal vascular occlusion in another. The latter was associated with reactive thrombocytosis, highlighting the susceptibility of damaged vascular beds to alterations in blood viscosity.

Despite their ophthalmological presentation, our patients gave histories revealing systemic disease, ANCA levels were raised, and investigations confirmed involvement of respiratory tract and kidneys in all but two. Our inclusion of two subjects (2, 10) with scleritis and raised ANCA titres, but without the full clinical criteria of Fauci *et al*,² reflects our view that this investigation may enable diagnosis earlier in the natural history of the disease. Both patients already had widespread vasculitis requiring systemic treatment.

CLINICAL ASSESSMENT

Although a careful history, and systemic and otolaryngological examination, exposed systemic inflammatory disease in our patients, further investigations were helpful in confirming the diagnosis and systems affected, and monitoring response to treatment.

Even in the absence of symptoms we frequently found radiological evidence of sinusitis or pulmonary cavitation. Renal impairment, which was found at presentation in most of our patients, was also always asymptomatic. Half the patients had significant proteinuria, and creatinine clearance was reduced in seven out of 10. Furthermore, renal disease was seen in patients with and without scleral necrosis: hence mild scleritis may be the presenting feature of incipient renal failure.

The activity of WG is reported to be better estimated by CRP than ESR,²² but both investi-

gations proved equally sensitive during the assessment and management of our patients. Seven subjects presented with an ESR of over 80 mm/h, and two of the remainder were already on steroid therapy. In addition there was usually anaemia, leucocytosis, and thrombocytosis.

Immune complexes, complement, and serum immunoglobulins were raised in some patients, but, as in other studies, these were not consistent findings.²³ One patient had a positive test for rheumatoid factor, but with the exception of ANCA other autoantibodies were not found in our patients.

The initiation of long term immunosuppressive therapy demands confident diagnosis of the underlying systemic disease. In this study the only diagnostic histology was obtained from nasal mucosal biopsy in one case after normal findings on otolaryngological examination. We consider this to be the most appropriate biopsy site in patients presenting with anterior ocular disease, even in the absence of upper respiratory symptoms. However, precise histological confirmation may still be difficult in both severe¹⁸ and early disease,²⁴ and inconclusive histology should never delay treatment.

As in previous reports¹⁸ the multifocal nature of this disease precluded the use of histology as a sole criterion for inclusion in our study. The ANCA titre (RIA) was increased in every case, usually at presentation but later in the course of the disease in two patients. Whenever it could be characterised by IIF, granular cytoplasmic staining was found, supporting the diagnosis of WG as opposed to other forms of vasculitis. The quantification of ANCA by RIA also provided a useful indicator of disease activity with which to monitor treatment.

TREATMENT

Oral steroids alone were insufficient to abort the progression of scleral necrosis. However, pulsed immunosuppressive therapy with intravenous methylprednisolone and cyclophosphamide successfully controlled scleritis whenever it was used. In the acute phase co-existing respiratory and renal disease had to be closely monitored, and two of our patients required plasma exchange because of progressive renal disease. Exacerbations were common, particularly following changes in treatment, but responded well to further pulsed immunosuppressive therapy.

Pulsed methylprednisolone and cyclophosphamide were well tolerated by all these patients. However, methylprednisolone therapy may be hazardous, and deaths have been reported.²⁵ The complications of prolonged oral prednisolone therapy are well known, and cyclophosphamide also has many side effects, including leucopenia,²⁶ haemorrhagic cystitis,²⁷ alopecia,²⁸ teratogenesis,^{29,30} and malignancy.³¹ Two of our patients developed profound cyclophosphamide-induced leucopenia, and in both cases this was followed by pneumonia.

We routinely check blood counts twice weekly during the inception of cyclophosphamide therapy, and monthly thereafter. However, the control of WG with immunosuppressive drugs may itself put a patient's life at risk, and many

ophthalmologists will wish to collaborate with physicians experienced in lymphocytotoxic therapy.

Ophthalmologists must be able to recognise the patient whose eye disease is the presenting feature of a life-threatening systemic vasculitis. Previous studies have described inexorable progression of the ocular disease in WG, but with prompt diagnosis and treatment of the underlying systemic disease this need not occur.

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- Godman GC, Churg J. Wegener's Granulomatosis. Pathology and review of the literature. *Arch Pathol* 1954; 58: 533-53.
- Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med* 1983; 98: 76-85.
- Walton EW. Giant cell granuloma of the respiratory tract (Wegener's granulomatosis). *Br Med J* 1958; ii: 265-70.
- Bullen CL, Liesegang TJ, McDonald TJ, DeRemee RA. Ocular complications of Wegener's granulomatosis. *Ophthalmology* 1983; 90: 279-90.
- Straatsma BR. Ocular manifestations of Wegener's granulomatosis. *Am J Ophthalmol* 1957; 44: 789-99.
- Brady HR, Israel MR, Lewin WH. Wegener's granulomatosis and corneoscleral ulcer. *JAMA* 1965; 193: 248-9.
- Austin P, Green WR, Sallyer DC, et al. Peripheral corneal degeneration and occlusive vasculitis in Wegener's granulomatosis. *Am J Ophthalmol* 1978; 85: 311-7.
- Spalton DJ, Graham EM, Page NGR, Sanders MD. Ocular changes in limited forms of Wegener's granulomatosis. *Br J Ophthalmol* 1981; 65: 553-63.
- Donald KJ, Edwards RL, McEvoy JDS. An ultrastructural study of the pathogenesis of tissue injury in limited Wegener's granulomatosis. *Pathology* 1976; 8: 161-9.
- Van der Woude FJ, Rasmussen N, Lobatto S, et al. Autoantibodies against neutrophils and monocytes; tool for diagnosis and marker for disease activity in Wegener's granulomatosis. *Lancet* 1985; i: 425-9.
- Gross WL, Ludeman G, Kiefer G, Lehmann H. Anti-cytoplasmic antibodies in Wegener's granulomatosis. *Lancet* 1986; i: 806.
- Savage COS, Jones S, Winearls CG, Marshall PD, Lockwood CM. Prospective study of radioimmunoassay for antibodies against neutrophil cytoplasm in the diagnosis of systemic vasculitis. *Lancet* 1987; i: 1389-93.
- Goldschmeding R, Huinink DTB, Faber N, et al. Identification of the ANCA antigen as a novel myeloid lysosomal serine protease. *APMIS* 1989; 97 (suppl 6): 46.
- Falk RJ, Jennett JC. Anti-neutrophil cytoplasmic autoantibodies with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing and crescentic glomerulonephritis. *N Engl J Med* 1988; 318: 1651-7.
- Cohen Tervaert JW, Goldschmeding R, Elema JD, et al. Autoantibodies against myeloid lysosomal enzymes in crescentic glomerulonephritis. *Kidney Int* 1990; 37: 799-806.
- Hollander D, Manning RT. The use of alkylating agents in the treatment of Wegener's granulomatosis. *Ann Intern Med* 1967; 67: 393-8.
- Harrison HL, Linshaw MA, Lindsley CB, Cuppage FE. Bolus corticosteroids for initial treatment of Wegener's granulomatosis. *JAMA* 1980; 244: 1599-600.
- Pinching AJ, Lockwood CM, Pussell BA, et al. Wegener's granulomatosis: observations on 18 patients with severe renal disease. *Q J Med* 1983; 52: 435-60.
- Meyer PAR, Watson PG, Franks W, Dubord P. 'Pulsed' immunosuppressive therapy in the treatment of immunologically induced corneal and scleral disease. *Eye* 1987; 1: 487-95.
- Watson PG, Booth Mason S. Fluorescein angiography in the differential diagnosis of sclerokeratitis. *Br J Ophthalmol* 1987; 71: 145-51.
- Watson PG. Vascular changes in peripheral corneal destructive disease. *Eye* 1990; 4: 65-73.
- Hind CRK, Winearls CG, Lockwood CM, Rees AJ, Pepys MB. Objective monitoring of activity in Wegener's granulomatosis by measurement of serum C-reactive protein concentration. *Clin Nephrol* 1984; 21: 341-5.
- Shillito EJ, Lehner T, Lessoff MH, Harrison DFN. Immunological features of Wegener's granulomatosis. *Lancet* 1974; i: 281-4.
- McCluskey RT, Fienberg R. Vasculitis in primary vasculitides, granulomatoses and connective tissue diseases. *Hum Pathol* 1983; 14: 305-15.
- Thompson JF, Chalmers DH, Wood RF, Kirkham SR, Morris PJ. Sudden death following high-dose intravenous methylprednisolone. *Transplantation* 1983; 36: 594-9.
- Fauci AS, Wolff SM, Johnson JS. Effect of cyclophosphamide on the immune response in Wegener's granulomatosis. *N Engl J Med* 1971; 285: 1493-6.
- Philips FS, Sterberg SS, Cronin AP, Vidol PM. Cyclophosphamide and urinary bladder toxicity. *Cancer Res* 1961; 21: 1577-89.
- Anonymous. Drug causes of hair loss. *Drug Ther Bull* 1978; 16: 77.
- Toledo TM, Harper RC, Moser RH. Fetal effects during cyclophosphamide and irradiation therapy. *Ann Intern Med* 1971; 74: 87-91.
- Greenberg LH, Verdes P, Tanaka KR. Congenital anomalies probably induced by cyclophosphamide. *JAMA* 1964; 188: 423-6.
- Marshall V. Premalignant and malignant skin tumours in immunosuppressed patients. *Transplantation* 1974; 17: 272-5.

The antineutrophil antibody in uveitis

D W Young

Abstract

Ninety eight patients with uveitis of various types were tested for the presence of the antineutrophil antibody or ANCA by an indirect immunofluorescence method. This antibody is found in patients with diseases associated with small vessel vasculitis, including Wegener's granulomatosis and microscopic polyarteritis. Eleven true positive cases were found. A positive test was not associated with the anatomical site of the uveitis but was related to the time course of the disease. In particular single/repeated rather than non-recurrent uveitis was associated with a positive test. Three groups of patients seem more likely to have positive tests: those with bilateral chronic posterior uveitis; a group with an anterior uveitis which is single/repeated who were younger than 46 at disease onset and had isolated eye disease; and an older group, aged 60 years or more at onset, with single/repeated uveitis and systemic features.

Over the years many antibodies have been discovered. Some, such as the antinuclear antibody for disseminated lupus erythematosus or rheumatoid factor for rheumatoid arthritis, are specific for a limited range of conditions, though neither are absolute markers for these conditions. Others, such as smooth muscle antibodies or parietal cell antibodies, are non-specific and frequently found in immune mediated diseases. They do not identify particular diseases.

In the early 1980s an antibody specific for neutrophil cytoplasm was recognised in diseases associated with systemic vasculitis.¹ Later this antibody was found to be a marker for a narrow range of conditions all associated with small vessel vasculitis.

Small vessel vasculitis is found in several diseases, including Wegener's granulomatosis,² microscopic polyarteritis,³ and segmental focal glomerulonephritis.¹ These conditions may all have the antineutrophil antibody (ANCA) as a common antibody. The antibody reacts against components of the neutrophil cytoplasm giving rise to a characteristic appearance on indirect immunofluorescence.⁴

The antineutrophil cytoplasmic antibody reaction can give one of three appearances, two of which, cytoplasmic and perinuclear, are regarded as positive. The third is a diffuse pattern, which is a non-specific reaction due to an excess of miscellaneous antibodies.

The cytoplasmic appearance is called C-ANCA. The 'C' is for classical, and it is most often found in Wegener's granulomatosis. The P-ANCA or perinuclear pattern occurs if neutrophil myeloperoxidase is exposed and combines with nucleic acid during the alcohol fixing stage. This reaction is more commonly found in

microscopic polyarteritis, though neither of these patterns are absolute for a particular disease.

Initially it seemed that the antibody might occur in only a limited number of conditions, but the list is expanding and now includes Kawasaki's disease,⁵ antglomerulobasement membrane disease,⁶ and the renal-pulmonary syndrome due to an IgM antibody.⁶ All have a small vessel vasculitis.

A survey of uveitis⁷ showed that in 44% of patients with anterior uveitis and in 9.6% of those with posterior uveitis no cause for their disease was found. Immunologically mediated mechanisms are possible when no cause is found.⁸

The uveal tract, particularly the choroid, is very vascular, and a vasculitis involving arterioles and venules is a common feature of uveitis. Against this background it seemed reasonable to look for the ANCA in patients with apparent idiopathic uveitis in the hope of either defining a disease mechanism, or deciding if conditions such as Wegener's granulomatosis or microscopic polyarteritis were present. Therefore patients attending an uveitis assessment clinic were screened for the ANCA.

Material and methods

The ANCA test was done by indirect immunofluorescence as recommended by the 1st ANCA workshop in Copenhagen in 1988.⁹ After anticoagulation with edetic acid (EDTA) diluted 1 in 2 with tissue culture medium, dextran 110 (CP Pharmaceuticals Ltd) was added. The blood was incubated for 30 minutes at room temperature, the white cell rich supernatant was harvested, and the cells were washed once in the medium and then centrifuged on to microscope slides (Cytocentrifuge Shandon) and fixed in 95% ethanol at 4°C for 5 minutes.

Test and control sera were incubated with the cells on the slides in a moist chamber for 30 minutes at room temperature. They were then washed for 20 minutes in a bath of phosphate buffered saline, pH 7.2, and incubated with a dilution of fluorescein isothiocyanate (FITC)-labelled anti-human IgG (Binding Site Ltd) for 30 minutes at room temperature. After a further period of washing, a drop of DABCO diazobicyclo-octane (Aldrich) was added and the slides were examined under a fluorescence microscope (Leitz).

The patients were referred from a general ophthalmology clinic with the diagnosis of uveitis, cause unknown. The anatomical site, time course, and activity of the inflammation were ascertained from the referral request, the patients' symptoms, and the blood test results.

All patients had a full clinical examination and a set of investigations including erythrocyte

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sedimentation rate (ESR), full blood count, and measurement of urea, electrolytes, liver function (bilirubin, alkaline phosphatase, aspartate), immunoglobulins, C reactive protein, antinuclear factor, rheumatoid factor, immune complexes, and immunoglobulins (IgA, IgG, IgM), and chest x ray and urine testing for protein, glucose, and blood.

Other investigations were done if they seemed relevant. These included a test for herpes virus antibodies, Kveim test, Mantoux test, tissue biopsy (lachrymal, nasal mucosa), test for toxocara, toxoplasma titres, and syphilis serology.

The type of uveitis was defined according to the site of the predominant signs and classified after the recommendations of the International Uveitis study Group¹⁰ with the modification that 'long non-recurrent' is called chronic. If two sites were of equal prominence, this was noted. Those patients with a posterior uveitis whose major lesion was a retinal vasculitis were listed separately in some of the tables.

The time course of the disease was divided into single/repeated when the duration of each episode was less than six months and chronic if it was greater.

A questionnaire reflecting the features of microscopic polyarteritis, Wegener's granulomatosis, and glomerulonephritis was put to the ANCA-positive patients.

On the basis of all the clinical and laboratory information the patients were divided into those with isolated eye disease (IED) and those with systemic features and eye disease (SED). χ^2 or Fisher's exact tests were used to test for statis-

tical significance. The two-sample *t* test was used to compare the ages of the ANCA-positive and negative group. Percentages in the tables were calculated across the rows.

Abbreviations used are AU anterior uveitis, IU intermediate uveitis, PU posterior uveitis, APMPE acute posterior multifocal placoid pigment epitheliopathy, RV retinal vasculitis.

Results

The total number of patients screened was 98, comprising 41 males and 57 females. Among these 19 positive tests were found; three had the cytoplasmic pattern, eight the perinuclear, and eight the diffuse. This last group are included in the negatives, giving 11 true positives and 87 negatives.

There were five males in the positive group and 36 in the negative as compared with six female positives and 49 negatives. The average age of the positive group was 42.7 years compared with 36.9 in the other group. None of these differences were statistically significant.

The distribution of the positives over the various anatomical sites for uveitis was broadly in proportion to the number of patients with that type of uveitis. No predilection for a particular site was revealed.

The difference in the proportion of positives with single/repeated over the chronic variety of uveitis gave a χ^2 of 4.11, significant at the 5% level. ANCA positives were found more often in single/repeated uveitis.

This analysis was repeated for the largest diagnostic group. AU which was single or repeated was found in 45 of the 98 patients. In this group there were six positive ANCA results. In the 19 patients with chronic AU no positives were found. Though this suggests an association, it was not statistically significant.

Every patient with a positive test had inflammatory changes in the anterior chamber at some stage of their disease. In a few the changes were minor compared to features in other parts of the eye, so the diagnosis of AU was not made. Patient 6 had 1+ of flare and a few cells in the anterior chamber for a short time, but there were overwhelming features typical of APMPE visible in the fundus.

Both types of ANCA responses were found, though the perinuclear pattern was more common. The sex ratio (five females and six males) was equal. The age of onset was wide. Five patients had other clinical features suggesting a systemic disease. These included Behçet's disease, mild colitis, polymyalgia rheumatica, interstitial lung disease, and non-specific ill health. Six patients appeared to have isolated eye disease.

In nine patients the ANCA test became negative as their eye disease settled.

Different groups were tested to see if the proportion of positives in those with only eye disease differed (IED) from those with eye disease and systemic features (SED). No differences were found between ANCA-positive and negative patients when tested over the whole group, those with single or repeated uveitis, or those with only anterior uveitis.

Table 1 Site of uveitis and ANCA test result

	AU (%)	PU (%)	AU+PU (%)	IP (%)	RV (%)
ANCA +ve	5 (45)	1 (9)	2 (18)	1 (9)	2 (18)
ANCA -ve	58	11	9	2	7
Total	64 (65)	12 (12)	10 (10)	3 (3)	9 (9)

Table 2 Time course of uveitis and ANCA result - all patients

	Single/repeated (%)	Chronic (%)
ANCA +ve	9 (82)	2 (18)
ANCA -ve	43	44
Total	52 (53)	46 (47)

Table 3 Summary of patients with ANCA positive

Patient	ANCA type	Sex	Onset	Uveitis type	IED/ SED	Persisting result
1	C	F	19	RV	S	No
2	C	M	21	AU B/R	I	No
3	C	F	54	RV	S	No
4	PN	M	8	AU+PU B/R	I	Yes
5	PN	F	12	AU+PU B/R	I	No
6	PN	M	32	APMPPE	I	No
7	PN	M	37	IU B/S	I	No
8	PN	M	45	AU U/S	I	No
9	PN	F	60	AU B/R	S	No
10	PN	M	70	AU B/R	S	Yes
11	PN	F	82	AU B/R	S	No

C=Cytoplasmic ANCA type. PN=perinuclear ANCA type. B=bilateral. U=unilateral. S=single. R=repeated.

Table 4 ANCA positives: cytoplasmic versus perinuclear responses

	Number	Male	Mean age	AU	AU+PU	IU/PU	IED	SED
Cytoplasmic	3	1	31.3	1	1	1	1	2
Perinuclear	8	5	44.8	4	2	2	5	3

The perinuclear group contained more males, was older, and had fewer systemic features than the cytoplasmic group. Two of the patients in the cytoplasmic group had posterior uveitis which was bilateral and chronic. This conjunction of C-ANCA-positive and chronic posterior uveitis seems to identify a separate subgroup of ANCA-positive patients with uveitis.

Discussion

Those tested do not form a random sample of patients with uveitis. Selection occurred at three levels: at referral from the community to the eye hospital by the general practitioner; by the ophthalmologist, who referred those patients who were causing concern because of their severity, their non-responsiveness to therapy, or the association of systemic features; and finally within the clinic no attempt was made to test systematically all patients. Those tested were the ones without an initial obvious cause for their condition such as sarcoid or tuberculosis.

Positivity of this test depends in some circumstances on the disease activity. It is used as a marker to monitor the progress of Wegener's granulomatosis.² The test was performed when the patients were seen in the assessment clinic, and this was usually one to four weeks after their initial presentation, often when the condition was settling. It is possible the number of positives was underestimated.

In nine patients the test changed from positive to negative as their condition improved. In two (4 and 10) the test was persistently positive irrespective of the eye disease activity.

Patient 4 developed anterior uveitis when aged 8. It has continued intermittently for 28 years. Apart from some joint swelling lasting a few days he has had no other symptoms. He may have a chronic vasculitis which is restricted to the eye. The other patient (10) has systemic features suggestive of a more generalised disorder.

Any clinical features outside the eye which might possibly be related either to the eye or to a disease affecting the eye labelled the patient as having a systemic condition. This was used to divide patients into those having isolated eye disease and those not. No evidence was found to link a positive test to systemic disease.

The proportion of positive tests, about 11%, was similar in patients with AU, PU, or AU plus PU. The site of the uveitis was not therefore associated with a positive test.

Analysis of the time course of uveitis (Table 2) shows that single/repeated uveitis was more frequently associated with positivity than chronic disease. This association was not found when AU alone was considered, though the results were suggestive. Possibly the size of the groups was not large enough to give statistical significance.

In the positive group there was no consistency in sex, age of onset, or association with other diseases, nor in type of ANCA response and any of these features. If it is assumed that all patients with a positive ANCA response have a small vessel vasculitis, then it follows this disease process does not cause a single type of uveitis.

Two explanations might account for the gross

variation in patients with positive results. Firstly, the test is totally non-specific and occurs in a wide variety of immune mediated diseases which produce an excess of antibodies of all types. Hence a wide variety of uveitides will occur. This view is unlikely. Many diseases can give rise to an occasional positive test, but consistent positives are found only in those conditions which have a small vessel vasculitis, suggesting a specific pathogenesis.

Alternatively the test does reflect a specific abnormality which gives rise to a single pathological process. However, there are many initiating factors for this process, and it may encompass patients of differing ages and associated diseases. This process can be manifested in different parts of the uveal tract, giving different anatomical sites for the uveitis. In a similar way other common pathogeneses may appear in different ways in the eye: consider the widespread features of ocular sarcoid, for example.

Wegener's granulomatosis and microscopic polyarteritis, which are most specific for the ANCA test, for unknown reasons cause different clinical responses in different patients, even though the pathological process is common. It is possible there is a common pathogenesis in ANCA-positive patients which gives rise to different clinical features.

At present it is not possible to make statements on the significance of a positive ANCA test, but certain pointers are evident. Perhaps the most interesting feature of this study was the association of a positive test and isolated uveitis tending to be single or repeated. Four patients (2, 4, 5, 8) fell into this group. However, the numbers are small, and statistical significance was not achieved for this association. This group may represent a small part of the high proportion of patients with AU in which no causative agent is found. A positive test does suggest there is a vasculitis caused by an antibody which cross reacts with elements of the neutrophil cytoplasm.

The two types of positive ANCA tests seem to identify three different groups of patients. The cytoplasmic response was associated with a chronic posterior uveitis manifested as a retinal vasculitis (patients 1, 3). The cytoplasmic response is normally associated with Wegener's granulomatosis. Both of these patients had systemic features; patient 1 had Behçet's disease, and patient 3 a mild colitis; neither had Wegener's granulomatosis.

The perinuclear positives fell into two groups. All had single/repeated disease, usually with an isolated AU, though some had intermediate or a posterior uveitis as well. The first group (4, 5, 7, 8) was younger (disease started before the age of 46 years) and without systemic features. The second group (9, 10, 11) was older, aged 60 years or more at onset, and associated with systemic features or diseases.

Eleven positive responders are rather a weak foundation for such suggestions, but they are offered as starting points for other investigators. Until the immune processes which cause uveitis are better defined, the role of this test will remain unclear. In a few it will help the diagnosis of microscopic polyarteritis nodosa, but in the

majority it will be an interesting though unexplained finding.

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- 1 Davies DJ, Moran JE, Niall JF, Ryan GB. Segmental necrotising glomerulonephritis with anti-neutrophil antibody: possible arbovirus aetiology? *Br Med J* 1982; 285: 606.
- 2 van der Woude FJ, Rasmussen N, Lobatto S, et al. Autoantibodies against neutrophils and monocytes: tool for diagnosis and markers of disease activity in Wegener's granulomatosis. *Lancet* 1985; i: 425-9.
- 3 Savage COS, Wineals CG, Evans DJ, Rees AJ, Lockwood CM. Microscopic polyarteritis: presentation pathology and progress. *Q J Med* 1985; 56: 467-89.
- 4 Rasmussen N, Wiik A. Indirect immunofluorescence examination for IgG-ANCA in sera submitted for 1st international workshop on ANCA 1988. *APMIS* 1989; 97 (suppl 6): 16-24.
- 5 Lockwood CM, Bakes D, Jones S, Whitaker KB, Moss DW, Savage COS. Association of alkaline phosphatase with an autoantigen recognised by circulating antineutrophil antibodies in systemic vasculitis. *Lancet* 1987; i: 716-20.
- 6 Pusey CD, Lockwood CM. Autoimmunity in rapidly progressive glomerulonephritis. *Kidney Int* 1989; 35: 929-37.
- 7 Henderly DE, Genstler AJ, Smith RE, Rao NA. Changing patterns of uveitis. *Am J Ophthalmol* 1987; 103: 131-6.
- 8 Anonymous. Change and progress in uveitis. (Editorial.) *Lancet* 1987; i: 19-21.
- 9 Wiik A. Delineation of a standard procedure for indirect immunofluorescence detection of ANCA. *APMIS* 1989; 97 (suppl 6): 12-3.
- 10 Saari KM. The international uveitis study group: classification of uveitis. *Acta Ophthalmol (Kbh)* 1984; 163 (suppl): 21-8.

FIFTY YEARS AGO

Mustard gas and its implications

DEAR SIRS,—In reply to Messrs. John Eyre and Frank W Law may I state that I have seen one drop of 4 per cent solution of hyd. perchlor. in glycerine accidentally fall on the cornea and in a few seconds which elapsed before washing out the conjunctival sac, severe and lengthy, but not permanent damage was inflicted on almost the whole of the corneal epithelium. Here there was no question of absorption. I quite agree with them that in the field of biology there is nothing more misleading than the argument from analogy, which indeed led eminent men to assume and publish results on the assumption that because man could accommodate the mammals could also.

But the argument from analogy hardly applies in this instance just quoted.

As regards the late effects of mustard gas on the cornea, the few cases I have seen showed deep seated infiltration rather than ulceration and there was very little clear cornea left anywhere. So that I doubt

whether either diathermy or contact glasses would have assisted. If such cases, which I am glad to say are rare, present themselves, the method suggested will be borne in mind. It is true that these conditions do recur without obvious cause. No one will be more grateful than myself if the writers have devised an effective treatment of mustard gas in the field, and will look forward to their publication of their experimental results. But the practical use of any remedy of the kind in advanced positions of any army is very difficult but not insuperable.

Some idea of the difficulty of acting efficiently in advanced stations may be learnt from the Palestine campaign, where towards the end men with high temperature were given quinine at once, no matter what seemed to be the cause of the temperature. If the medical officers had waited until they could be sure that malaria was the cause it would at times have been too late. To neutralise the effects of mustard on the eyes, special instruction for the forward units will be a necessity. — Letter from James W Barrett. *Br J Ophthalmol* 1941; 25: 95.

Distinguishing features of the iridocorneal endothelial syndrome and posterior polymorphous dystrophy: value of endothelial specular microscopy

Hania C Laganowski, Emil S Sherrard, Malcolm G Kerr Muir, Roger J Buckley

Abstract

The literature suggests that posterior polymorphous dystrophy (PPD) may show features such as iridocorneal adhesions, glassy membranes, and pupillary ectropion which are typically ascribed to the iridocorneal endothelial (ICE) syndrome. This complicates diagnosis. PPD, unlike ICE, is familial, and ICE, unlike PPD, is usually progressive and frequently complicated by glaucoma: thus it is important to distinguish between them. To determine whether this could be achieved by specular microscopy, since the posterior corneal surface is abnormal in both conditions, 57 cases of ICE and 44 of PPD were repeatedly examined and photographed with the specular microscope. Progressive and/or static morphological features of the corneal endothelium and Descemet's membrane were found that were specific for each condition. Specular microscopy can thus provide a definitive diagnosis of ICE or PPD even in uncertain cases.

The iridocorneal endothelial or ICE syndrome, which comprises Chandler's syndrome (CHS), progressive iris atrophy (PIA), and the iris naevus (Cogan-Reese) (INS) syndrome, is a non-familial, usually unilateral anomaly of the posterior cornea and iris, the aetiology of which is unknown.¹

Posterior polymorphous dystrophy, or PPD, is generally regarded as an inherited, frequently bilateral abnormality of the posterior, non-banded layer of Descemet's membrane, which implies that it is congenital and the result of an anomaly of the corneal endothelium at about the time of birth.²

The ICE syndrome is typically symptomatic and is most commonly diagnosed in middle age. It is progressive and is frequently complicated by glaucoma and/or corneal decompensation.

Posterior polymorphous dystrophy has been diagnosed in all age groups, usually as an incidental finding, since it is typically asymptomatic. It is commonly non-progressive; only occasionally is it associated with corneal decompensation or glaucoma.²

The universal clinical sign of the ICE syndrome is a finely hammered silver appearance^{3,4} of all or part of the posterior corneal surface when viewed in specularly reflected light with the slit-lamp. When only part of the posterior corneal surface appears as hammered silver, the remaining areas of endothelium are composed of either enlarged or exceptionally small cells.⁵⁻⁷ Dystrophic iris changes are almost always present. These range

from subtle stromal melting (as in CHS) to full thickness iris 'melt' and/or 'stretch' holes (as in PIA) and the formation of constricted nodules on the anterior iris surface (as in INS). Peripheral anterior synechiae commonly occur and are often accompanied by corectopia and ectropion uveae. A glassy membrane may be visible bridging part of the anterior chamber angle and adhering to the anterior surface of the iris.

Classically the diagnosis of PPD requires the presence of small, round, discrete, transparent, vesicular lesions, surrounded by a ring of opacity, at the level of Descemet's membrane.⁸ Other features in addition to vesicles are present in many corneas, and this has led to subdivision of PPD into descriptive categories.² Vesicular PPD implies the presence of vesicles alone; these may be single, scattered, or grouped. A variant in which large and numerous patches of confluent vesicles occur is termed geographic PPD by some authors.^{2,9} Band PPD is characterised by elongated, broad, band(s) of roughened Descemet's membrane delineated by narrow, opaque, irregular ridges. Diffuse PPD involves all or a large part of the posterior corneal surface and appears as swirled patterns of irregular thickening and opacification of Descemet's membrane; it is often accompanied by full-thickness corneal oedema. Apart from a statement by Waring *et al*¹⁰ that the endothelium over the PPD lesions is altered and an inference that it is normal elsewhere, there appears to be no published description of the endothelium in PPD as seen with the slit-lamp.

Many of the clinical features which are typically ascribed to the ICE syndrome, such as broad peripheral iridocorneal adhesions, a glassy membrane on the iris surface, pupillary ectropion and raised intraocular pressure, have been reported in cases of PPD.^{2,8,9,11-13} Indeed Cibis *et al*¹³ state that some patients with PPD 'meet the diagnostic criteria of Chandler's syndrome'.

If there is an overlap of the clinical signs of ICE and PPD it raises the possibility that the two conditions are related. If this were so, then PPD should be regarded as potential ICE, which is associated with a higher incidence of complications, most significantly glaucoma, and ICE should be sought in the families of patients with PPD with a view to instituting early treatment.

The possible occurrence of ICE-like features in PPD may make its 'clinical differentiation from ICE difficult'.¹⁴ The iridocorneal endothelial syndrome, which is non-familial, in general has a poorer outlook for the affected individual than does PPD, which, being inherited, has implications for the family. Therefore it is important to distinguish between ICE

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and PPD at the clinical level to establish the correct prognosis and overall management (treatment, follow-up, screening) for the patient and his or her relatives. As a means to this end it has been suggested that the corneal signs of PPD are sought in the families of patients in whom a diagnosis of CHS is being considered.¹³ However, while inherited traits are significant, their disclosure is time consuming and expensive. Moreover, the finding of PPD vesicles in family members of patients with classic signs of ICE does not necessarily constitute a diagnosis of PPD in those patients, as suggested by some authors.⁸ It would be preferable and more precise if the distinction between ICE and PPD could be based only on the clinical signs of the patients. Since an anomaly of the corneal endothelium probably underlies both disorders and many of the corneas affected by either remain clear for many years, if not indefinitely, endothelial specular photomicroscopy (ESP) has the potential to reveal features at the cellular level which may distinguish between ICE and PPD.

This communication compares and contrasts the ESP findings in 57 cases of the ICE syndrome with those in 44 cases of PPD.

Material and methods

All the patients in this series were selected from those referred with a probable clinical diagnosis of ICE or PPD to a special study group. Selection was based on the slit-lamp appearance of each case. To be included in the series as ICE depended on the presence of a hammered silver appearance of the posterior corneal surface and the absence of vesicles and, as PPD, on the presence of classic vesicles in one or both eyes with or without other features of PPD.

The 57 cases of ICE comprised 37 with progressive iris atrophy, 18 with Chandler's syndrome, and two with iris naevus syndrome. All were unilateral.

In accordance with the subdivision outlined by Waring *et al*¹ 19 of the 44 cases of PPD were classified as vesicular PPD. Of these, 15 were bilateral, one was unilateral, and three were monocular, to give a total of 34 affected eyes. Twenty-three cases were classed as band PPD. Posterior polymorphous dystrophy bands (in addition to vesicles) were present in both eyes in four and in one eye in 19 cases. Of the latter the other eye showed vesicles alone in five cases and was normal in the remaining 14. Of the 27 eyes with PPD bands 23 had a single band and four had two. Two cases, both bilateral, were classed as diffuse PPD.

None of the eyes with PPD showed the iris or anterior chamber angle changes typically associated with ICE, or any other ocular abnormality.

The Pocklington, Keeler/Konan large field specular microscope was used throughout the study. At least 15 specular photomicrographs were taken of the posterior corneal surface of each affected eye, and a representative sample of pictures was taken of the contralateral normal eye in unilateral cases. Many of the cases were similarly examined on multiple occasions at six-monthly intervals over several years.

Results

The ESP appearances are here summarised; they have been described in detail elsewhere.^{7,15}

IRIDOCORNEAL ENDOTHELIAL SYNDROME

In all cases of the ICE syndrome specular microscopy revealed the presence of abnormal cells (Fig 1), characterised by a dark area with a light central spot and often a light peripheral zone. Sometimes dark cell margins were visible. The cells varied in size but typically were larger than normal endothelial cells. They occurred in the areas that appeared as hammered silver with

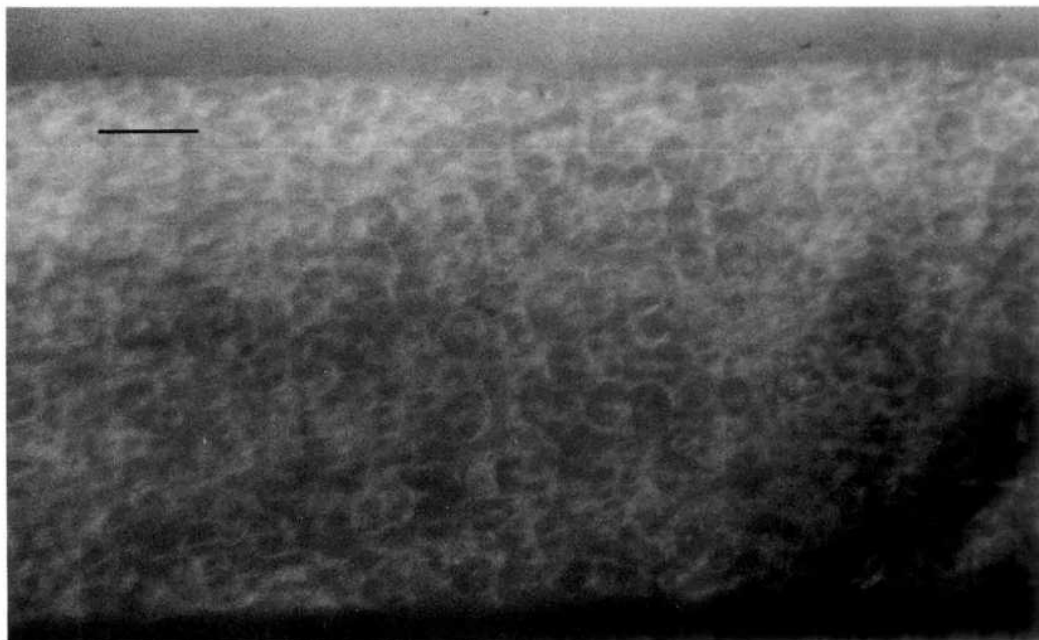


Figure 1 Specular photomicrograph of typical ICE cells, which appear as a negative of normal endothelium, from a case of total ICE. (Bar=0.1 mm.)

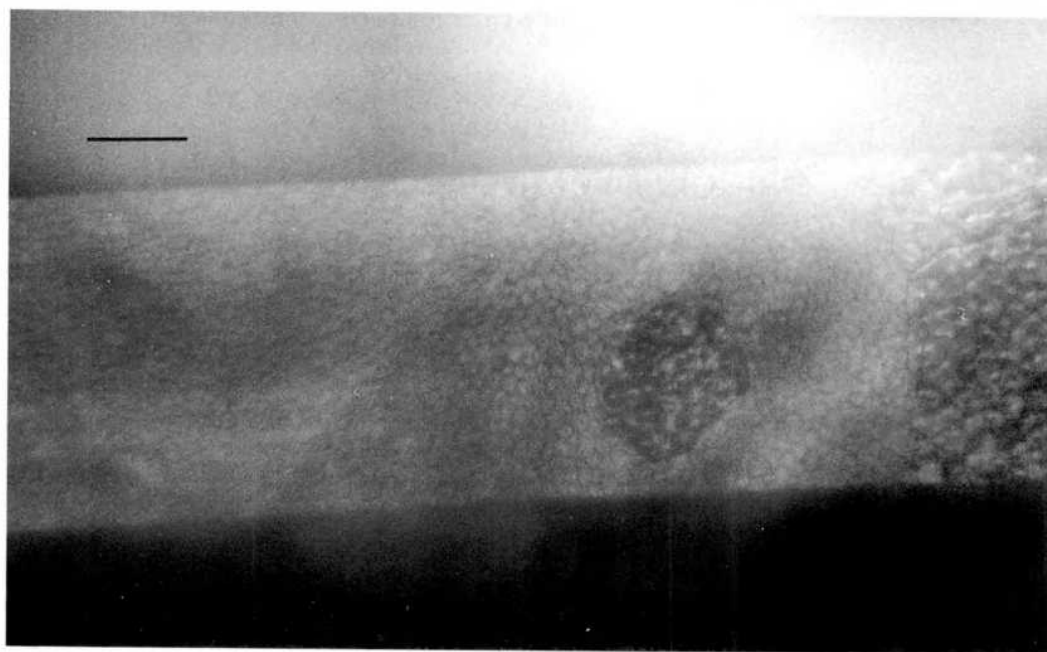


Figure 2 Specular photomicrograph of subtotal ICE plus showing ICE tissue (right-hand side) clearly demarcated from endothelium composed of very small, distinct cells. An isolated patch of ICE tissue (an ICE-berg) lies within the endothelium distorting adjacent cells. (Bar=0.1 mm.)

the slit-lamp. These cells are regarded as pathognomonic of the ICE syndrome and so have been termed ICE cells and the tissue they form ICE tissue.⁷

The ICE cells or tissue and the remaining endothelial cells formed four basic patterns:⁷

(1) Disseminated ICE occurred in seven cases. It showed ICE cells scattered throughout a vaguely defined endothelial mosaic which was made up of larger than average cells.

(2) Total ICE (Fig 1) was found in 17 cases. Here the entire posterior corneal surface was covered by ICE tissue and no normal endothelium was apparent.

(3) Subtotal ICE plus (Fig 2) occurred in 23 cases. It was characterised by an area of clearly defined ICE tissue which covered from one to

three-quarters of the posterior corneal surface and tended to extend to, or arise from, beyond the limbus. The inner edge of the ICE tissue was frequently sinuous and formed an abrupt junction with the remaining endothelium. Occasionally a small patch of ICE tissue was isolated in the endothelium forming what has been termed an ICE-berg⁷ (Fig 2). Endothelial cells were distinct and very small with a significantly greater cell population density than in age matched normal eyes. The cells adjacent to the ICE tissue were often elongated parallel to its edge (Fig 2).

(4) Subtotal ICE minus was found in 10 cases. Here a mass of ICE tissue merged often imperceptibly with the remaining endothelium, which was composed of greatly enlarged cells.

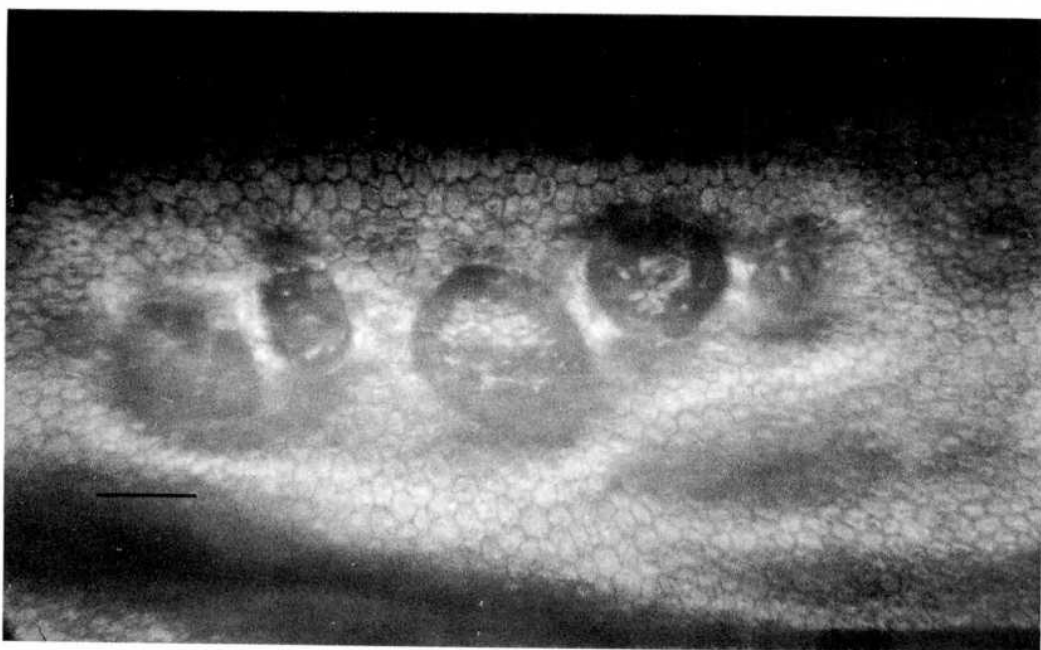


Figure 3 Specular photomicrograph of classic PPD vessicles appearing as clearly defined, dark rings. Endothelial cells 'within' and 'without' the rings are parafocal and enlarged and undistorted. (Bar=0.1 mm.)

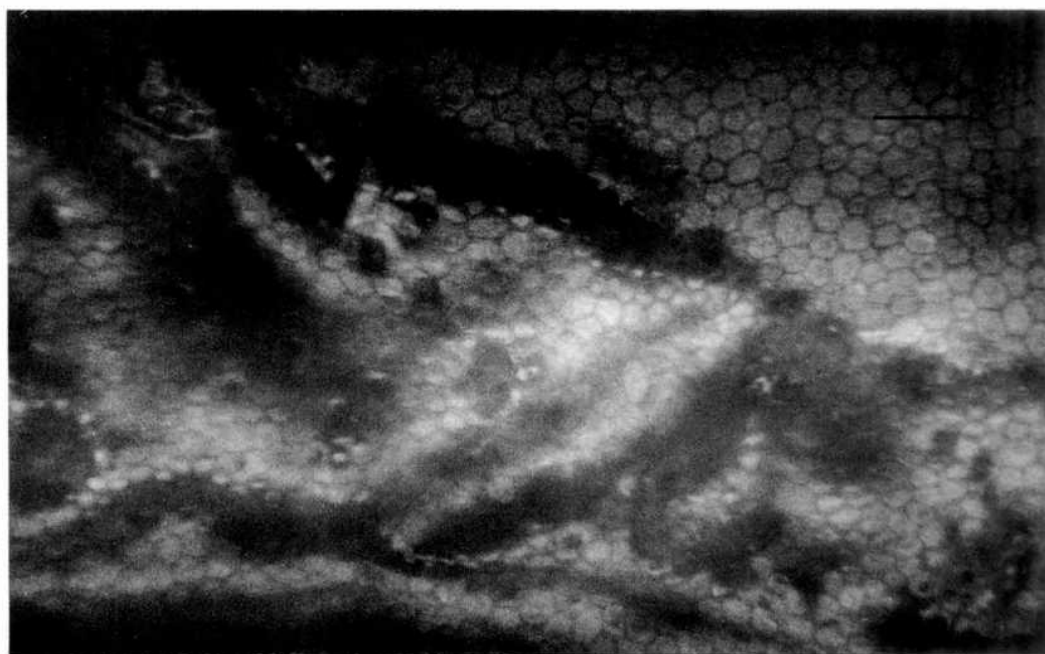


Figure 4 Specular photomicrograph of PPD band showing endothelium on a strip of roughened Descemet's membrane delineated by dark borders. Endothelial cells 'within' and 'without' the band are parafocal and greatly enlarged; many 'within' and on the borders are masked. (Bar=0.1 mm.)

Follow-up examination over several years revealed that all cases originally classed as disseminated ICE progressed to total ICE with an associated accelerated loss of cells. No significant changes occurred in total ICE. In the subtotal variants there were changes in contour of the ICE tissue, but the population density of ICE cells remained relatively constant, while in cases of subtotal ICE plus there was a significant increase in the CPD of the endothelium.

POSTERIOR POLYMORPHOUS DYSTROPHY

With the specular microscope classic PPD vesicles appeared as dark rings with distinct, often scalloped edges surrounding a lighter, mottled centre (Fig 3). The relief image^{16,17} of vesicles indicated that they were shallow, steep sided pits in the posterior aspect of Descemet's membrane. A variable number of small black spots often studded the endothelium and were interpreted as representing miniature vesicles.

In the specular, and relief mode, a PPD band appeared as a strip of roughened Descemet's membrane delineated by dark, frequently scalloped, approximately parallel borders (Fig 4). In many examples these were apparently composed of coalesced black discs (giving a similar appearance to the black rings of vesicles) (Fig 4) and sometimes of confluent, small, complete vesicles. In others the appearance of the overall band was of a row of coalesced, large vesicles. A band usually terminated in separate or clusters of vesicles.

In the cases of diffuse PPD the entire posterior corneal surface was affected by swirled patterns of irregular features that were suggestive of distorted, incomplete, confluent vesicles.

In all cases of vesicular and band PPD recognisable endothelial cells were visible over the entire posterior corneal surface, including the vesicles and bands. Over the lesions, how-

ever, particularly on their dark, delineating borders, the image of the cells was often diminished, indistinct, or partly masked because of optical effects of the lesions, but the cells were not physically distorted (Figs 3, 4).

The endothelium 'within' and 'without' vesicles and bands was parafocal (Figs 3, 4). This indicates that it bridges rather than lines them. This in turn suggests that vesicles and bands are filled.

The endothelial cell population density was reduced in all but three of the cases of vesicular PPD and was even lower in all cases of band PPD compared with age matched normal subjects. In the cases of diffuse PPD visible endothelial cells were slightly larger than normal in one and were of normal size in the other.

Follow-up examination over several years revealed no changes in the situation or configuration of PPD vesicles or bands. There was no evidence of an accelerated rate of loss of endothelial cells.

Discussion

Recent reports^{2,8,9,11-13} of the macroscopic features of the ICE syndrome and PPD occurring together in an individual or separately in different members of a family have raised the possibility of a link between the two conditions. They have also led to confusion and disagreement about the diagnostic criteria.

Prior to these reports ICE and PPD have been regarded as separate dystrophies because of various differences between their modes of presentation, propensity for progression, final outcome, and, classically, their distinctive slit-lamp appearances. Moreover, histopathological studies, though based only on decompensated corneas from each condition, reveal differences in Descemet's membrane which make a relationship between ICE and PPD highly unlikely.¹⁸

A comparison of the specular microscopical findings of the posterior corneal surface in this series of cases of ICE and PPD appears to distinguish between the two conditions at the clinical level. No case of PPD showed ICE cells. Although ICE-birgs and PPD vesicles may appear to be analogous, an ICE-birg consists of a nest of ICE cells, surrounded by a thin dark edge, lying within the endothelium and distorting those cells adjacent to it (Fig 2), while a PPD vesicle is a pit delineated by a thick, dark border and lying anterior to recognisable endothelial cells without distorting them (Fig 3). PPD vesicles and bands were shown to be fixed features of the posterior cornea. ICE cells and tissue, including ICE-birgs, however, were not stable, particularly in the disseminated variant. Endothelial cells were recognisable as such in both conditions, but in ICE they were most commonly much smaller (Fig 2), while in PPD they were almost always much larger than normal (Figs 3, 4).

The ESP findings in classic cases of ICE and PPD were specific for each condition. On the basis of this study, therefore, it is suggested that, while the two conditions may conceivably coexist in the same eye or in different members of the same family, the ICE syndrome and PPD are distinct entities. It is concluded that ICE and PPD should be diagnosed on corneal signs alone. While the appropriate signs usually can be seen with the slit-lamp, ESP, by revealing ICE cells and distinguishing between ICE-birgs and PPD vesicles, will always provide a definitive diagnosis even in uncertain cases and thus promote accurate management of patients and their families.

- 1 Shields MB. Progressive essential iris atrophy, Chandler's syndrome and the iris-naevus (Cogan Reese) syndrome: a spectrum of disease. *Surv Ophthalmol* 1979; 24: 3-20.
- 2 Waring GO, Rodrigues MM, Laibson PR. Corneal dystrophies: II. Endothelial dystrophies. *Surv Ophthalmol* 1978; 23: 147-68.
- 3 Chandler PA. Atrophy of the stroma of the iris, endothelial dystrophy, corneal oedema and glaucoma. *Am J Ophthalmol* 1956; 41: 607-15.
- 4 Hirst LW, Quigley HA, Stark WJ, Shields MB. Specular microscopy of iridocorneal endothelial syndrome. *Am J Ophthalmol* 1980; 89: 11-21.
- 5 Bourne WM. Partial corneal involvement in the iridocorneal endothelial syndrome. *Am J Ophthalmol* 1982; 94: 774-81.
- 6 Neubauer L, Lund OE, Leibowitz HM. Specular microscopic appearance of the corneal endothelium in iridocorneal endothelial syndrome. *Arch Ophthalmol* 1983; 101: 916-8.
- 7 Sherrard ES, Frangouli MA, Kerr Muir MG, Buckley RJ. The posterior surface of the cornea in the irido-corneal endothelial syndrome: a specular microscopical study. *Trans Ophthalmol Soc UK* 1985; 104: 766-74.
- 8 Cibis GW, Krachmer JA, Phelps CD, Weingeist TA. The clinical spectrum of posterior polymorphous dystrophy. *Arch Ophthalmol* 1977; 95: 1529-37.
- 9 Hirst LW, Waring GO. Clinical specular microscopy of posterior polymorphous endothelial dystrophy. *Am J Ophthalmol* 1983; 95: 143-55.
- 10 Waring GO, Laibson PR, Rodrigues MM. Clinical and pathologic alterations of Descemet's membrane: with emphasis on endothelial metaplasia. *Surv Ophthalmol* 1974; 18: 325-68.
- 11 Waring GO, Bourne WM, Edelhauser HF, Kenyon KR. The corneal endothelium: normal and pathologic structure and function. *Ophthalmology* 1982; 89: 531-90.
- 12 Boruchoff SA, Kuwabara T. Electron microscopy of posterior polymorphous degeneration. *Am J Ophthalmol* 1971; 72: 879-87.
- 13 Cibis GW, Krachmer JA, Phelps CD, Weingeist TA. Iridocorneal adhesions in posterior polymorphous dystrophy. *Ophthalmology* 1976; 81: 770-7.
- 14 Boruchoff SA, Weiner MJ, Albert DM. Recurrence of posterior polymorphous corneal dystrophy after penetrating keratoplasty. *Am J Ophthalmol* 1990; 109: 323-8.
- 15 Laganowski HC, Sherrard ES, Kerr Muir MG. The posterior corneal surface in posterior polymorphous dystrophy: a specular microscopical study. *Cornea* in press.
- 16 Sherrard ES, Buckley RJ. The relief mode: new application of the corneal specular microscope. *Arch Ophthalmol* 1982; 100: 296-300.
- 17 Hartmann C. Die 'indirekte' Spiegelmikroskopie: eine neue Technik zur In vivo Untersuchung der Hornhauttrübsache. *Ophthalmologica* 1981; 183: 177-86.
- 18 Alvarado JA, Murphy CG, Juster RP, Hetherington J. Pathogenesis of Chandler's syndrome, essential iris atrophy and the Cogan-Reese syndrome: II. Estimated age at disease onset. *Invest Ophthalmol Vis Sci* 1986; 27: 873-82.

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REFERENCES: 1 Jones H, Ekberg NL. *Lett N Eng J Med* 1979; **301**: 270.

2 Levy NS, Boone L, Ellis E. *Glaucoma* 1985; **7**: 54-62.

3 Schoene RB, Abuan T, Waid RL, Beasley CH. *Am J Ophthalmol* 1984; **97**: 86-92.

4 Van Buskirk EM. *New Trends in Ophthalmol* 1986; **104**: 1178-1184.

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Changes in keratometry following trabeculectomy

Charles E Hugkulstone

Abstract

The results of keratometry following trabeculectomy are presented. In contrast to the effects of wound gape after cataract extraction, trabeculectomy produces a reduction in the vertical corneal radius. An initial corresponding increase in horizontal radius is found immediately postoperatively, but this is not apparent by two and seven weeks after surgery. A possible explanation for these findings is proposed.

Corneal astigmatism following cataract extraction is now well recognised.¹⁻⁴ The aetiology is thought to be the result of wound compression or wound gape^{2,4} and also may be related to the size of the incision.³

Since 1968⁵ trabeculectomy has become the operation of choice for glaucoma. However, there have been no reports of its effects on astigmatism. I wish to present the findings of a study of the short-term changes in corneal curvature following trabeculectomy.

Material and methods

Ten consecutive patients undergoing trabeculectomy were enrolled. There had been no previous ocular surgery to the eye studied. All gave verbal consent for this investigation.

Trabeculectomy was performed under either local or general anaesthesia. A limbal based conjunctival flap was raised and reflected forward. A square partial-thickness scleral flap (approximately 5×5 mm) was dissected towards the limbus, and a wedge of tissue was excised from beneath this. A peripheral iridectomy was performed, and the scleral flap was secured with either two or five 9/0 virgin silk sutures. The conjunctiva was closed with a continuous 6/0 catgut suture.

Keratometry readings were taken of the central cornea by means of the Allergan Humphrey autokeratometer. Both eyes were carefully aligned with reference to the markers on the headrest of the instrument, and the machine was focused according to the manufacturer's instructions. Readings were taken preoperatively, then at one and three days and two and seven weeks postoperatively. At the same

times the visual acuity and intraocular pressure were recorded.

To assess any variations that may have occurred because of technique three keratometry readings were also obtained from a control group – a baseline value and also readings at one and three days after the initial measurement. Again, these eyes were required to have had no previous surgery.

All postoperative keratometry readings were compared with the preoperative values by the paired *t* test. Results are given as mean (SD).

Results

The 10 patients undergoing trabeculectomy consisted of five men and five women. Their mean age was 67.2 (7.4) years. All required drainage surgery for poorly controlled chronic open-angle glaucoma. One patient was unable to fixate on the alignment target of the keratometer on the first postoperative day but was otherwise able to complete this study. Therefore the number of subjects for the first postoperative day is nine, while it is 10 for all other times.

Table 1 shows the mean vertical and horizontal corneal radii (in mm) and the angle of the vertical meridian (in degrees) for the study group. The postoperative vertical radii are all significantly less than the preoperative value ($p<0.05$ at 1 day, $p<0.02$ at 3 days and 2 weeks, and $p<0.05$ at 7 weeks). The horizontal radii are greater than the preoperative reading at days 1 and 3 ($p<0.005$), but there is no significant difference between values at 2 or 7 weeks in comparison with those obtained preoperatively. The angle of the vertical meridian showed no postoperative change from the baseline reading.

Six patients had the scleral flap closed with two sutures and four with five sutures. Although these numbers are too small for meaningful statistical analysis, there did not appear to be any differences in either group's behaviour in comparison with that of the overall group.

There was no correlation between the keratometry readings and the intraocular pressure at each time interval. There was also no correlation between the final visual acuity and the change in both vertical and horizontal corneal radii. Since mydriatic drops were used over the first two weeks postoperatively, only the final visual acuity was compared with the preoperative value, and there was no significant difference.

The control group consisted of five patients

Table 1 Mean (SD) vertical and horizontal corneal radii (mm) and angle of vertical meridian (degrees) in the trabeculectomy group

	Vertical radius	Horizontal radius	Vertical angle
Preop.	7.71 (0.29)	7.73 (0.25)	95.0 (22.5)
1 Day	7.36 (0.52)	8.03 (0.32)	100.9 (13.3)
3 Days	7.43 (0.39)	8.06 (0.31)	91.9 (18.6)
2 Weeks	7.60 (0.33)	7.79 (0.33)	94.0 (16.9)
7 Weeks	7.53 (0.36)	7.72 (0.21)	102.4 (16.5)

Table 2 Mean (SD) vertical and horizontal corneal radii (mm) and angle of vertical meridian (degrees) in the control group

	Vertical radius	Horizontal radius	Vertical angle
Baseline	7.68 (0.27)	7.70 (0.19)	104.4 (32.1)
1 Day	7.68 (0.27)	7.69 (0.19)	110.8 (23.0)
3 Days	7.71 (0.27)	7.69 (0.21)	101.0 (31.9)

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(three women and two men) who were undergoing cataract extraction to the fellow eye. Their mean age was 68.4 (13.0) years. Table 2 shows the results for this group. There were no differences between any of these values in comparison with the baseline readings.

Discussion

Wound gape following cataract extraction has been shown to produce an increase in the vertical corneal radius.^{2,4} Since trabeculectomy also produces a form of wound gape, a similar change would be expected postoperatively. The surprising finding in this study was that there was in fact a reduction in the corneal radius in the vertical meridian.

An explanation for this difference in behaviour in comparison with cataract extraction may be the result of the partial-thickness scleral flap created during trabeculectomy. The wound gape that may follow cataract extraction is placed between sutures, with no more than conjunctiva over it. In trabeculectomy the surgically produced gap is overlaid by a scleral flap. This is capable of spreading any support from the sutures inserted into it over the whole of the wound gape. In cataract sections, however, any tension produced by the sutures is to either side of the site of wound gape, with little, if any, support given by the overlying conjunctiva. In addition the more posterior placement of the incision in trabeculectomy may also help to explain the observed difference in behaviour in comparison with cataract extraction.

This cannot be the entire explanation, as the reduction in corneal radius following cataract surgery has been shown to be the result of wound compression by overtight sutures.^{1,2,4} However, as in this study, the scleral flap sutures in trabeculectomy are not usually inserted under undue tension.

The lack of any difference between scleral flaps sutured with two or five stitches suggests that this spreading of tension is the result of the scleral flap itself rather than the number of sutures, and it offers support for the above explanation. However, the numbers in these two subgroups are small.

The corresponding changes in the horizontal radii following trabeculectomy also suggest a

different mechanism of astigmatism from that after cataract extraction. In the present study there was a decrease in the vertical radius and an increase in the horizontal radius during the first three days postoperatively. However, at two and seven weeks postoperatively the change in the vertical radius was not accompanied by a corresponding change in the horizontal radius. A previous study of postcataract astigmatism found that 45.2% of cases showed a similar decrease in the vertical radius with an increase in the horizontal radius at one week.³ However, by one month 42.2% showed an increase in vertical radius with a corresponding decrease in horizontal radius, whilst none had a decrease in vertical radius and increase in horizontal radius.

Although the changes in curvature affected the central cornea and achieved statistical significance, they were not reflected in any marked change in visual acuity by the end of the study. No assessment of the changes in refraction were made, but for the same reason these are unlikely to be of any major importance.

No noteworthy changes occurred in the control group, which suggests that the observed changes were not due to poor technique in the use of the autokeratometer.

In conclusion, the changes in corneal curvature after trabeculectomy do not appear to behave in the same manner as they do after cataract extraction. However, this is a small scale study, and further research is required to confirm these findings. In addition, long term studies are needed to investigate whether these changes continue to evolve, as has been shown to occur after cataract extraction.⁶

My grateful thanks are due to Mr T Arulampalam and Mr A S Rubasingham for kindly allowing me to study patients under their care.

- 1 Jaffe NS, Clayman HM. The pathophysiology of corneal astigmatism after cataract extraction. *Ophthalmology* 1975; 79: 615-30.
- 2 Van Rij G, Waring GO. Changes in corneal curvature induced by sutures and incisions. *Am J Ophthalmol* 1984; 98: 773-83.
- 3 Reading VM. Astigmatism following cataract surgery. *Br J Ophthalmol* 1984; 68: 97-104.
- 4 Wishart MS, Wishart PK, Gregor ZJ. Corneal astigmatism following cataract extraction. *Br J Ophthalmol* 1986; 70: 825-30.
- 5 Cairns JE. Trabeculectomy. Preliminary report of a new method. *Am J Ophthalmol* 1968; 66: 673-9.
- 6 Parker WT, Clorfeine GS. Long-term evolution of astigmatism following planned extracapsular cataract extraction. *Arch Ophthalmol* 1989; 107: 353-7.

Comparison between Heparin
surface modified IOLs and
normal IOLs in the same patient.



This female has a history of
longstanding diabetes and
glaucoma.

A. Slit lamp

B. Specular microscopy

Right eye — NORMAL
PMMA LENS

- 11 months post-operatively
- Confluent giant cells can be
seen clearly on both slides



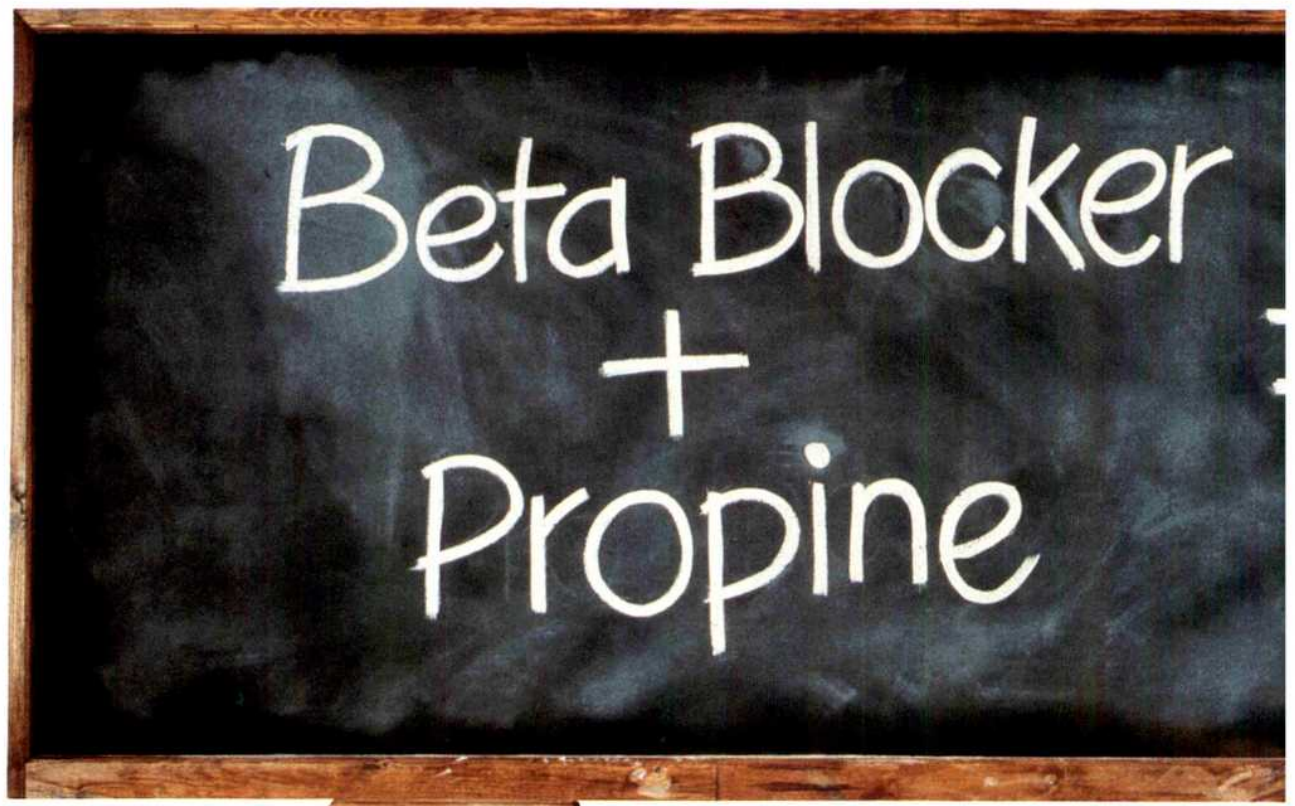
C. Slit lamp

D. Specular microscopy

Left eye — HEPARIN
SURFACE MODIFIED LENS

- 6 months post-operatively
- No giant cells
- Newton's rings seen clearly

A clear case
for Heparin
surface modified
IOLs.

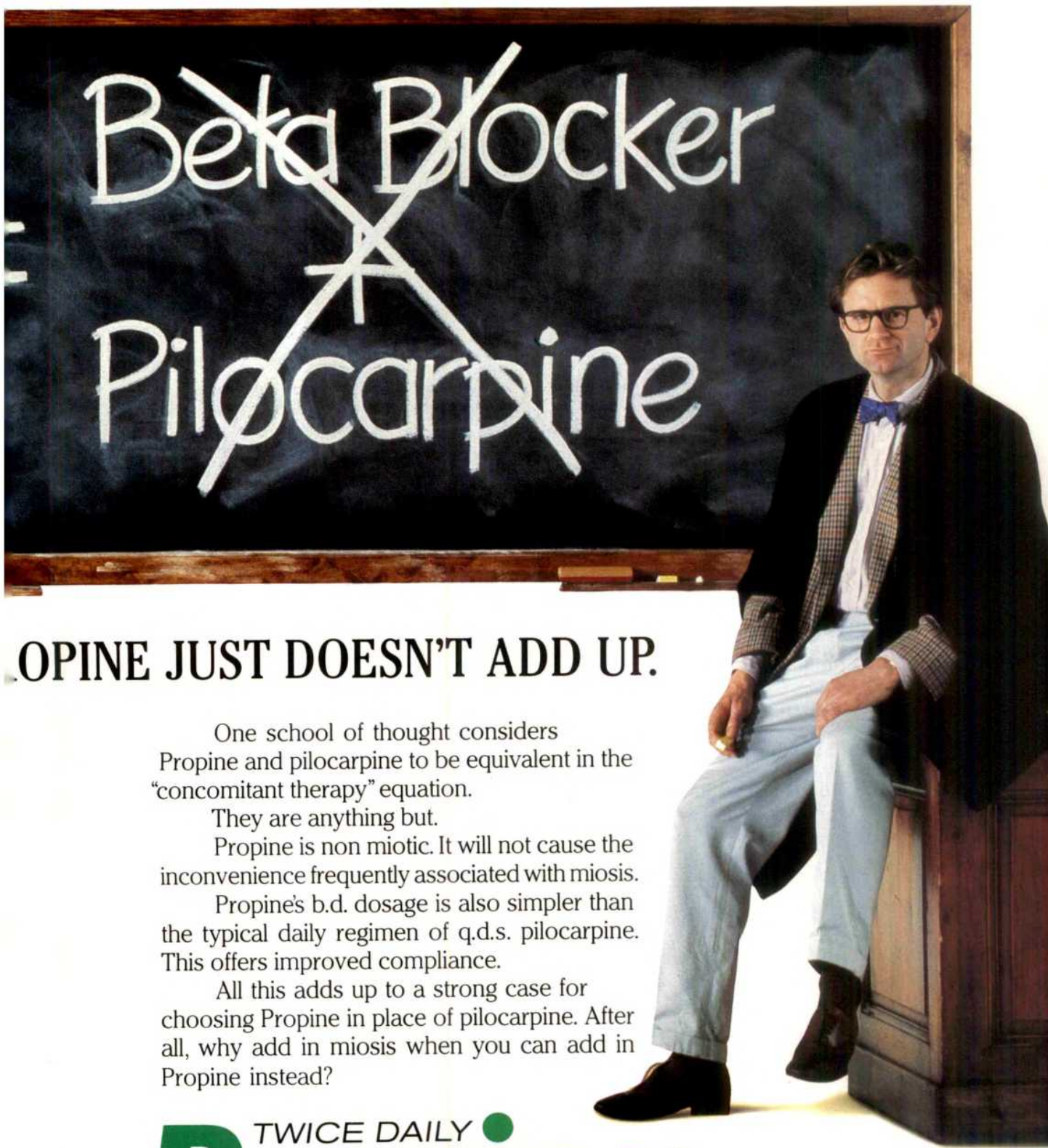


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Presentation Sterile ophthalmic solution containing dipivefrin hydrochloride USP 0.1% (w/v). Also contains benzalkonium chloride Ph Eur 0.005% (w/v), disodium edetate Ph Eur 0.015% (w/v), with sodium chloride Ph Eur and purified water Ph Eur. **Uses** Propine is indicated for the reduction of intraocular pressure in chronic open angle glaucoma or ocular hypertensive patients with anterior chamber open angles. **Dosage and administration** The usual dosage is one drop in the affected eye(s) every 12 hours. **Contra-indications, warnings, etc.** *Contra-indications:* Patients suffering from angle closure glaucoma. *Use in pregnancy:* the safety of intensive or protracted use of dipivefrin

during pregnancy has not been substantiated. *Precautions:* Dipivefrin should be used with caution in patients with narrow angles since dilation of the pupil may trigger an attack of angle closure glaucoma. Macular oedema is a rare occurrence with adrenergic use in aphakic patients. Prompt reversal generally follows discontinuance of the drug. Macular oedema with dipivefrin does present as a possibility in the aphakic patient. The product contains benzalkonium chloride and should not be used by patients continuing to wear soft (hydrophilic) contact lenses. *Side-effects:* Cardiovascular: Tachycardia, arrhythmias and hypertension have been reported with ocular administration.



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aline, and may occur rarely with Propine therapy. Ocular: the most frequently
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nd vasodilation, mydriasis and allergic reactions, including blepharoconjunctivitis,
een reported occasionally. Adrenochrome deposits in the conjunctiva and cornea
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ed during long term therapy with Propine. The condition is reversible upon discon-
ce of the drug. **Pharmaceutical precautions** Store at room temperature. Discard
used contents 28 days after opening the bottle. **Legal category** POM. **Package**

quantities Plastic dropper bottle containing 10ml. **Further information** The active ingre-
dient in Propine, dipivefrin HCl, is a prodrug of adrenaline. Its lipophilic nature facilitates
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Basic NHS cost: (as at February 1990) £4.89. **Date of preparation** February 1990.

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Pituitary adenomas: automatic static perimetry and Goldmann perimetry. A comparative study of 345 visual field charts

Michèle Grochowicki, Alain Vighetto, Serge Berquet, Yadh Khalfallah, Geneviève Sassolas

Abstract

In a series of 81 cases of pituitary adenoma 345 charts of visual field performed with static automatic perimetry (AP) on the Vision Monitor and Goldmann perimetry (GP) were compared. Generally both methods were equivalent in the detection of chiasmal compression. The charts were divided into two groups: (A) 208 charts and (B) 137 charts according to the number of isoptres investigated: two (V4, 112) or three (V4, 112, 12). In group A the AP was more often altered than the GP, and the difference was statistically significant ($p < 0.001$). In group B the GP seemed more effective, but the number of questionable cases was greater and the difference was not statistically significant. When the most internal isoptre of GP was outside the central 30°, AP was more often abnormal (29%) than GP (2.2%), and the difference was statistically significant (χ^2 , $p < 0.001$). Within the central 30° the GP seemed more often to be altered (23% of cases) than the AP (19.4%), but one-third of the cases were questionable. Within the central 30° both techniques gave identical results and there was no statistically significant difference. The discrepancies between both static and kinetic techniques are an argument for their complementary use.

Goldmann perimetry (GP) remains the reference method in neuro-ophthalmic investigations despite the advance of automatic perimetry (AP). Many studies have been reported on AP in the assessment of chiasmal compression.¹⁻⁹ But the role of AP remained a matter of debate¹⁰ because of clinical and physiopathological considerations. Goldmann perimetry was reported to be less tiring for the patients than AP^{5,10} and easier to perform when the fixation was poor.⁵ Comparison of different studies of automatic static perimetry is difficult because of the many types of apparatus on the market and the different techniques used, namely, liminal or supraliminal. For example, Meienberg *et al*¹¹ stated that the frequent occurrence of relative defects in chiasmal lesions was a circumstance favouring a quantitative liminal method, but Wirtshafter and Coffman³ found that a supraliminal AP could 'at least equal the performance of an experienced perimetrist using manual Goldmann kinetic . . . in the detection of visual field defects resulting from chiasmal tumors.'

We studied the visual fields of 81 patients with pituitary adenomas by both techniques, Goldmann and automatic static perimetry. For the latter we used a fast-thresholding programme,

tested previously in the investigation of various neuropathies.^{12,13}

Patients and methods

Eighty-one patients with pituitary adenomas were examined in our Clinic of Neuro-ophthalmology from June 1987 to June 1989. All patients with surgical and immunocytochemical confirmation of the diagnosis were included. We also included non-surgically treated patients whose evidence on a CT scan and/or magnetic resonance imaging (MRI), biological perturbations highly suggestive of pituitary adenoma, and a correlation between the volume of the tumour and the degree of the hormonal hypersecretion. We excluded patients with a previous ophthalmological disease such as chronic glaucoma, cataract, and retinal disease, or who were known to have an associated disease possibly altering the visual field, such as multiple sclerosis. We also excluded nearly blind patients and patients with a serious intellectual deterioration. GP and AP were performed as part of a comprehensive battery of ophthalmological investigations described elsewhere.^{12,13}

The investigation of the visual field combined a GP study with two (V4, 112) or three (V4, 112, 12) isoptres with a static AP study. The last was carried out on the Vision Monitor. The fast-thresholding programme coupled a 4-2-2-2 foveolar threshold determination⁸ to a relative suprathreshold (4dB) strategy for the 94 other points scattered within the central 30°. Its sensitivity and clinical acceptability seemed to us to be a good compromise. This programme allowed a clear mapping of the blind spot. The patients had one or more visual fields. Each chart corresponded to the visual field of one eye.

The analysis of the charts was undertaken by three of us, two ophthalmologists (MG, SB) and one neurologist (AV), who classified them separately. The analysis of the charts was performed technique by technique. The results of the biological and radiological studies were concealed, but the observers knew that the patients had pituitary adenoma. The analysis was qualitative and topographic.¹⁴ The evaluation of scotomas had been previously carried out.¹² We considered as 'questionable' the cases in which the defect of the visual field was isolated and in contradiction to the results of other ophthalmic tests and to the surgical and the radiological assessments.

A comparison was undertaken between 345 charts with AP and 345 with GP performed on the same day in the same patient. Two groups were specified according to the number of

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isoptres used for the Goldmann perimetry and compared with the corresponding AP. Group A included 208 charts with two isoptres (V4, 112), group B 137 charts with three isoptres (V4, 112, 12). Group B was smaller either because the smallest isoptre, 12, was not looked for during the examination or because it was impossible to detect it (25% of the patients).

Finally a topographic and comparative study was made between 345 charts of AP with 345 charts of GP in accordance with the most internal isoptres in GP regardless of their number. Two groups were specified according to the position of the most internal isoptre of GP – outside the central 30° (n=93) and inside the central 30° (n=252).

Results

Comparison between the charts of the visual fields with AP and GP, n=345 (Table 1)

We recorded the charts as one of the two alternatives 'normal' or 'abnormal'. With this study of the paired alternatives in 79.7% of the eyes the visual fields were evaluated by both methods in the same way as 'normal' (31.9%) or 'abnormal' (47.8%). AP was found to be altered alone (37 eyes) slightly more often than the GP (33 eyes), but the difference was not statistically significant ($\chi^2=0.228$).

Comparison of AP and GP according to the number of the isoptres of GP (Table 2)

Group A, GP with 2 isoptres compared with AP (n=208). – AP and GP were equivalent in 63.5% (132 eyes). In 30.3% of cases (63 eyes) the charts made with AP displayed more defects than those with GP. The difference was statistically highly significant (χ^2 test, $p<0.001$). In a few cases (13 eyes, 6.2%) there were more abnormalities on the GP than on the AP.

Group B; GP with three isoptres compared with AP (n=137). – In 77 eyes (56.2%) the visual fields were identical by both methods. The Goldmann perimetry was more altered than the AP in 34.3% (47 eyes) but the number of questionable cases increased and the difference was not statistically significant. In a few cases (13

Table 2 Comparisons of automatic perimetry (AP) and Goldmann perimetry (GP) according to the number of the isoptres of GP

	Group A V4, 112	Group B V4, 112, 12
Visual field charts	n=208	n=137
Identical	132	77
AP and GP	63.5%	56.2%
Isolated or predominant alteration of AP:	63	13
Increase of defect area	30.3%	9.5%
Temporal notch	39	2
Quadrantal defect	18 (6*)	8 (3*)
Isolated or predominant alteration of GP:	6	3
Increase of defect area	13	47
Temporal notch	6.2%	34.3%
Quadrantal defect	6	22
	7 (3*)	15 (8*)

*Questionable cases.

eyes, 9.5%) the defects were larger with AP than with GP.

Topographic study according to the position of the most internal isoptres of GP (Table 3)

AP and GP were identical in 68.8% and 60.3% of eyes according to the position of the most internal isoptre of GP, respectively outside and inside the central 30°. When the most internal isoptre of GP was outside the central 30°, AP was more often abnormal (29%) than GP (2.2%), and the difference was statistically significant (χ^2 test, $p<0.001$). Within the central 30° the GP was apparently altered more often (23% of cases) against 19.4% for AP, but one-third of the cases were 'questionable'. Within the central 30° both techniques were identical, and there was no significant difference statistically.

Discussion

In our study in nearly 80% of the eyes the visual fields were evaluated in the same way by both methods as normal or abnormal (Table 1). When only two isoptres were investigated, AP seemed to be superior to GP in disclosing more important defects than Goldmann perimetry or even a defect neglected by it. The results were reversed when three isoptres were used. But the use of this third index I2 was not always feasible even in a normal subject, and the evident rise in results of GP was linked with a rise of 'questionable' results (16/47). When the most internal of the Goldmann isoptres was outside the 30°, AP was more effective (Table 3). In contrast, when it was

Table 1 Comparison between the charts of the visual fields with automated perimetry (AP) and Goldmann perimetry (GP): n=345. Study of the paired alternatives

Visual field charts	n=345
Identical AP and GP	110
Normal	31.9%
Abnormal	165
Abnormal AP and normal GP	47.8%
Quadrantal anomalies: simple defect or extense scotoma:	37
Superotemporal quadrant	10.7%
Inferotemporal quadrant	22
Nasal quadrant	12
Extensive, nasal and temporal	3
General depression	5
Isolated relative central scotomas	2
Multiple relative central scotomas without	7
Systematisation	6
Abnormal GP and normal AP	2
Notch on superotemporal quadrant	33
General depression	9.5%
	32
	1

Table 3 Topographic study according to the position of the most internal isoptre of Goldmann perimetry

Visual field charts	Out. 30° n=93	Ins. 30° n=252
Identical	64	145
AP and GP	68.8%	60.3%
Isolated or predominant alteration of AP:	27	49
Increase of defect area	29%	19.4%
Temporal notch	9	32
Quadrantal defect	12	14
Isolated or predominant alteration of GP:	6	3
Increase of defect area	2	58
Temporal notch	2.2%	23%
Quadrantal defect	2	(1/3*)
	2	28
	2	20
	–	10

*Questionable case.

Outer 30°=outside the central 30°; ins. 30°=inside the central 30°.

inside the 30° the results of GP were better than AP but the number of 'questionable' cases increased (1/3), and both methods seemed to be equivalent.

The problem of the qualitative analysis of these visual field data was whether to consider as pathological or not a slight defect in the superotemporal quadrant. This was especially evident for Goldmann perimetry with an important number of questionable cases. Knowing that the patient was suspected of having a pituitary adenoma impressed the perimetrist as much in his carrying out Goldmann perimetry as it did the ophthalmologist in his analysis of the visual field. The standardisation of the visual fields recorded with AP suppressed the perimetrist's bias but evidently not the observer's knowledge. In general we found better interobserver agreement with AP than with GP (data in preparation), though the interpretation of small defects at the limit of eccentricity (temporal notch) remained problematic.

Good concordance has been reported¹²³⁵⁶ in the interpretation of both AP and GP (between 66 and 83% of cases). The correlation between automatic perimetry and Goldmann perimetry was good either with a liminal²⁵⁶ or with a supraliminal³ technique, whatever the device used – Dicon,³ Humphrey,⁵ or Octopus.¹²⁶ But a quantitative comparison was frequently impossible.⁷ The results changed with the number of isoptres used, with the Goldmann perimeter and the clinical conditions of the examination.

An important feature of our results may be the thorough investigation of the internal 30°. It was emphasised by Frisen,¹⁵ who found 'a bitemporal foreshortening of central isoptres, not extending beyond 15 degrees of eccentricity as an early sign of mid chiasmal compression.' He also thought that these defects seemed to be more difficult to detect in static profiles. In a comparative study of static and kinetic perimetry on the same device Charlier *et al*⁸ stressed that kinetic perimetry appeared to be more sensitive in the detection of small scotomas located over 15° of eccentricity. But the interest of a static central investigation of the visual field was demonstrated in the lesions compressing the anterior visual pathway,¹⁶ and the association of both methods is mandatory for investigating the statokinetic dissociation.¹⁷ The

discrepancies between both static and kinetic techniques were an argument for their complementary use.

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- 1 Li SG, Spaeth GL, Scimeca HA, Schatz NJ, Savino PJ. Clinical experiences with the use of an automated perimeter (Octopus) in the diagnosis and management of patients with glaucoma and neurologic diseases. *Ophthalmology* 1979; 86: 1302-12.
- 2 McCrary JA III, Feigon J. Computerized perimetry in neuro-ophthalmology. *Ophthalmology* 1979; 86: 1287-301.
- 3 Wirtschaffner JD, Coffman SM. Comparison of manual Goldmann and automated static visual fields using the Dicon 2000 perimeter in the detection of chiasmal tumors. *Ann Ophthalmol* 1984; 16: 733-41.
- 4 Bynke H, Krakau CET. A modified computerized perimeter and its use in neuro-ophthalmic patients. *Neuro-ophthalmology* 1981; 2: 105-15.
- 5 Beck RW, Bergstrom TJ, Lichter PR. A clinical comparison of visual field testing with a new automated perimeter, the Humphrey field analyzer, and the Goldmann perimeter. *Ophthalmology* 1985; 92: 77-82.
- 6 De Natale R, Cannavo S. Computerized perimetry in the early diagnosis of hypophyseal microadenoma. *Acta XXV Concilium Ophthalmologicum. Proceedings of the XXVth International Congress of Ophthalmology, Rome, May 4-10, 1986.* Amsterdam, Berkeley, Milan: Kugler, 1987: 1748-51.
- 7 Ambühl J, Mattle H, Seiler R. Visual fields in patients with pituitary tumors. In: Heijl A, ed. *Proceedings of the VIIIth International Perimetric Society Meeting.* Amsterdam, Berkeley, Milan: Kugler and Ghedini, 1988-9: 127.
- 8 Charlier JR, Defoort S, Rouland JF, Hache JC. Comparison of automated kinetic and static visual fields in neuro-ophthalmology patients. In: Heijl A, ed. *Proceedings of the VIIIth International Perimetric Society Meeting.* Kugler and Ghedini, 1988-9: 3-8.
- 9 Dannheim F, Roggenbuck C. Comparison of automated conventional and spatial resolution perimetry in chiasmal lesions. In: Heijl A, ed. *Proceedings of the VIIIth International Perimetric Society Meeting.* Amsterdam, Berkeley, Milan: Kugler and Ghedini, 1988-9: 377-82.
- 10 Glaser JS. The optic chiasm. In: Lessels S, van Dalen JTW, eds. *Current neuro-ophthalmology.* Year Book Medical, 1988; 1: 53-66.
- 11 Meienberg O, Mattle H, Jenni A, Flammer J. Quantitative versus semiquantitative perimetry in neurological disorders. *Proceedings of the 6th International Visual Field Symposium.* Dordrecht: Junk, 1985: 233-7.
- 12 Grochowicki M, Vighetto A, Pissavin C. Pseudotumor cerebri. Longitudinal study using contrast sensitivity and automated static perimetry. *Neuro-ophthalmology* 1990; 10: 97-108.
- 13 Vighetto A, Grochowicki M, Cousin J. La sensibilité au contraste spatial dans la sclérose en plaques. *Rev Neurol (Paris)* 1990; 146: 264-70.
- 14 Dubois-Poulsen A. *Le champ visuel. Topographie normale et pathologie de ses sensibilités.* Paris: Masson, 1952.
- 15 Frisen L. The earliest visual field defects in mid-chiasmal compression. In: Heijl A, Greve EL, eds. *Proceedings of the 6th International Visual Field Symposium.* Dordrecht: Junk, 1985.
- 16 Trobe JD, Glaser JS. Quantitative perimetry in compressive optic neuropathy and optic neuritis. *Arch Ophthalmol* 1978; 96: 1210-6.
- 17 Safran AB, Glaser JS. Statokinetic dissociation in lesions of the anterior visual pathways. A reappraisal of the Riddoch phenomenon. *Arch Ophthalmol* 1980; 98: 291-5.

Effect on mydriasis of modifying the volume of phenylephrine drops

E W Craig, P G Griffiths

Abstract

The cardiovascular effects of topically administered phenylephrine 10% are well known and can be minimised by reducing the concentration of drops administered. By modifying the dimensions of the dropper tip we reduced the volume of the drops administered, and therefore the total dose of phenylephrine, without altering the concentration. No difference in the mydriasis produced by drops of small and normal volume could be detected. Since a smaller dose of phenylephrine is administered with smaller drops, the risk of systemic side effects could be reduced by modifying the tips of eyedroppers.

The existence of systemic side effects from topically administered drugs is well recognised. Particular problems arise with topical β blockers such as timolol, and with phenylephrine, a commonly used mydriatic. Several different adverse reactions have been reported following topical ocular administration of phenylephrine 10%. These include severe hypertension, subarachnoid haemorrhage, ventricular arrhythmias, and myocardial infarction.¹ The dose of phenylephrine administered can be reduced by using more dilute drops such as phenylephrine 2.5%. We adopted an alternative approach of using eyedrops of the same concentration, but reduced volume, delivering a smaller total dosage.

Materials and methods

Normal sized drops were delivered by means of Minims of 10% phenylephrine. Drop volume was determined by squeezing 10 drops on to the pan of a Sartorius 1212 MP balance. The weight of each drop was determined by dividing by 10. This was repeated 25 times, a new Minim being used each time. It is assumed that the drops have the same density as water and the weight in milligrams can be directly converted to volume in microlitres.

Reduced volume drops were produced by means of a 22G Venflon intravenous cannula which was attached to the end of a Minim after removal of the central stylette (Fig 1). The

volume of the drop obtained was determined as described previously.

Pupil size was determined photographically. The subjects had their left pupil photographed while holding a millimetre scale on the lower lid within the field of view of the camera. The size of the pupil could then be determined on the projected image of colour slides, since the magnification factor would be the same for the pupil and the scale. The measurements were made without knowing what sized drop had been administered.

All photographs were taken at a constant level of illumination while the subject focused on letters at 3 m distance to ensure a constant amount of accommodation. Ametropes were excluded because magnification factors would be introduced when photographing through a spectacle lens. Informed consent was obtained from 20 healthy volunteers who had their left pupil photographed before receiving a small or a large drop, and a second photograph was taken one hour later. Half of the subjects received a small drop first and half received a large drop first; an interval of one week was left between tests.

Results

The normal volume of drops from Minims of phenylephrine 10% was 30 (SD4) μ l. Attaching a 22G Venflon intravenous cannula reduced the drop volume to 10 (SD2) μ l.

Most subjects commented that the smaller drops caused much less discomfort and were not always even aware that they had been instilled. The results are summarised in Table 1. The mean pupillary dilatation produced by normal sized drops was 3.6 (SD 1.2) mm and the mean pupillary dilatation from small drops was 3.7 (SD 0.9) mm. The small difference between these figures is not statistically significant ($t > 1$, $df = 19$, $p > 0.1$).

Discussion

Phenylephrine is a powerful sympathomimetic drug which is an almost pure α receptor agonist. Systemically administered phenylephrine leads to peripheral vasoconstriction, resulting in increased systolic and diastolic blood pressure and reflex bradycardia. Heathe and Giete² have shown that topical phenylephrine 10% increases blood pressure by up to 10 mmHg in 2% of subjects. Despite this, reports of side effects in the adult population are rare in view of its widespread use, though recently myocardial infarction was described following its intraoperative use.³

The normal volume of the tear film is 7 μ l – namely, 1 μ l in the precorneal tear film and 3 μ l in

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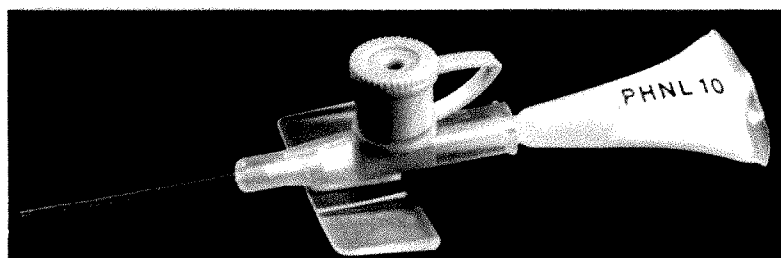


Figure 1 Showing attachment of 22 gauge cannula to a Minim of phenylephrine.

Table 1 Pupillary dilatation produced by 30 µm and 10 µm eyedrops

Subject	Pupil size, mm			Pupil size, mm		
	Pre-drop	Post-30 µl drop	Difference	Pre-drop	Post-10 µl	Difference
1	5.0	9.0	4.0	5.5	9.5	4.0
2	5.5	8.0	2.5	5.0	8.0	3.0
3	4.0	7.0	3.0	4.5	8.5	4.0
4	5.0	7.5	2.5	5.0	7.5	2.5
5	3.5	8.5	5.0	3.0	7.5	4.5
6	4.0	8.0	4.0	4.0	7.5	3.5
7	3.0	7.0	4.0	3.0	7.0	4.0
8	4.5	5.5	1.0	4.0	6.0	2.0
9	3.0	6.5	3.5	3.5	6.5	3.0
10	6.0	7.5	1.5	6.0	7.0	1.0
11	3.0	8.0	5.0	3.0	7.5	4.5
12	3.5	7.0	3.5	4.0	7.0	3.0
13	4.5	9.0	4.5	4.5	8.0	3.5
14	4.0	8.0	4.0	4.0	8.0	4.0
15	4.0	8.0	4.0	4.0	8.0	4.0
16	4.0	6.0	2.0	4.0	8.5	4.5
17	5.5	8.5	3.0	5.0	8.5	3.5
18	3.0	7.5	4.5	3.0	7.0	4.0
19	4.5	9.0	5.5	5.5	8.5	3.0
20	4.0	8.5	4.5	4.0	8.5	4.5
Mean pupillary dilatation 3.6 (SD 1.2) mm				Mean pupillary dilatation 3.7 (SD 1.2) mm		

each of the tear menisci. This can briefly increase to a maximum of 30 µl.⁴ Shell⁴ has estimated that 80% of the volume of a 50 µl drop rapidly passes down the nasolacrimal duct, so that most of the administered drug has minimal contact time with the eye and passes to the highly vascular nasal mucosa, where it can be systemically absorbed. Absorption across the conjunctiva and nasal mucosa avoids first-pass metabolism in the liver and results in peak levels only 10 minutes after topical administration.⁵

The accepted safe dose of intravenous phenylephrine is 1.5 mg.³ A 50 µl drop of phenylephrine contains 5.0 mg, so that systemic absorption can easily lead to dangerously high levels, particularly when multiple drops are given. Fortunately the volume delivered by Minims is not the 50 µl which is widely quoted, but only 30 µl. Nevertheless there is still further scope for reduction in drop size, as the 10 µl drops were just as effective as 30 µl drops.

Reducing drop size may increase bioavailability of the medication. Patton and Robinson⁶ have shown that 5 µl of 1.92 × 10⁻² M pilocarpine produced the same tear film concentration as 25 µl of 1.0 × 10⁻² M despite containing only 38% as much pilocarpine. This could be because the smaller drops stimulate less lacrimation and so

increase contact time. One of the limiting factors in reducing the size of eyedrops is ease of administration. It was difficult to ensure that only one drop fell on to the eye from the 22G cannula, and the lack of awareness that a drop has been delivered could cause problems.

A thin-walled cannula of the type used in this study would be quite unsuitable for commercial use, as it would be damaged too easily, and it tends to deliver a jet of fluid if the bottle or Minim is squeezed too hard. Conventional eye dropper tips which have an inner resistance aperture to ensure that single drops are delivered, and a relatively thick wall in relation to the diameter of the lumen, can be modified to deliver consistently smaller drops.^{7,8}

Reducing the volume of eyedrops is not the only way to reduce systemic absorption: punctal plugging, nasolacrimal duct compression, and lid closure after eyedrop instillation are all effective.^{9,10} However, these techniques require prolonged commitment from medical staff and exceptionally well motivated patients. They would in any case be even more effective after administration of a small drop, since the cornea across which absorption into the eye occurs occupies only 17% of the ocular surface area,¹¹ so that there is still a significant area through which systemic absorption can occur.

1 Fraunfelder FT, Scafadi M. Possible adverse effects from topical ocular 10% phenylephrine. *Am J Ophthalmol* 1978; **4**: 447-53.
2 Heath P, Geite CW. Use of phenylephrine hydrochloride (neo-synephrine hydrochloride) in ophthalmology. *Arch Ophthalmol* 1949; **41**: 172.
3 Yoon-Kee Lai. Adverse effect of intraoperative phenylephrine 10%; case report. *Br J Ophthalmol* 1989; **73**: 468-9.
4 Shell JW. Pharmacokinetics of topically applied drugs. *Surv Ophthalmol* 1982; **26**: 207-18.
5 Kumar V, Schoenwald DS, Chien BS, Packer AJ, Choi WW. Systemic absorption and cardiovascular effects of phenylephrine drops. *Am J Ophthalmol* 1985; **99**: 180-4.
6 Patton TF, Robinson JR. Quantitative precorneal disposition of topically applied pilocarpine nitrate in rabbit eyes. *J Pharm Sci* 1976; **65**: 1295-9.
7 Brown RH, Hotchkiss ML, Davis BE. Creating smaller eyedrops by reducing eyedropper tip dimensions. *Am J Ophthalmol* 1985; **99**: 460-4.
8 Brown RH, Lynch MG. Design of eyedropper tips for topical beta blocking agents. *Am J Ophthalmol* 1986; **102**: 123-4.
9 Zimmerman TJ, Kooner KS, Kandarakis AS, Ziegler LP. Improving the therapeutic index of topically applied ocular drugs. *Arch Ophthalmol* 1984; **102**: 551-4.
10 Huang TC, Lee DA. Punctal occlusion and topical medications for glaucoma. *Am J Ophthalmol* 1989; **107**: 151-5.
11 Watsky MA, Jablonsky MM, Edelhauser HF. Comparison of conjunctival and corneal surface areas in rabbits and humans. *Curr Eye Res* 1988; **7**: 483-7.

Prevalence of migraine in low-tension glaucoma and primary open-angle glaucoma in Japanese

Tomoaki Usui, Kazuo Iwata, Motohiro Shirakashi, Haruki Abe

Abstract

We studied the prevalence of migraine in low-tension glaucoma (LTG) and primary open-angle glaucoma (POAG). Seventy seven Japanese patients with LTG, 73 with POAG, and 75 normal subjects were randomly selected and tested with a headache questionnaire. The prevalence of headache with or without typical migrainous features (unilateral headache or ocular pain, nausea, vomiting, and visual disturbance before headache) was 51% in LTG, 42% in POAG, and 44% in normal patients. The prevalence of headache with two migrainous features or more (probable migraine) was 17% in LTG, 11% in POAG, and 12% in normal subjects. The prevalence of headache with three migrainous features (classical migraine) was 5% in LTG, 3% in POAG, and 3% in normal subjects. There was no statistically significant difference in the prevalence of any types of migraine between the three groups of patients ($p > 0.05$). These results suggest there is no significant relationship between migraine and LTG or POAG in Japanese patients.

Low-tension glaucoma (LTG) is characterised by glaucomatous optic disc cupping and visual field loss in eyes that have consistently normal intraocular pressures, open angles, and the absence of any contributing ocular or systemic disorders. The clinical features of LTG resemble those of primary open-angle glaucoma (POAG) except for the absence of increased intraocular pressure.

The pathogenesis of LTG is still uncertain. Several investigators have reported that LTG and POAG have different aetiologies,¹ and others have reported that LTG is a variant of POAG.² Recently Phelps *et al*³ studied the prevalence of migraine in patients with LTG, POAG, ocular hypertension, and normal subjects using a headache questionnaire, and reported a significant relationship between migraine and LTG: a higher prevalence of migraine in patients with LTG than in other groups of patients. Drance⁴ and Ederer⁵ found their data convincing. In the present study, using the identical headache questionnaire as used by Phelps and Corbett,³ we studied the prevalence of migraine in normal subjects and in Japanese patients with LTG and POAG.

Patients and methods

We gave the headache questionnaire to 91 randomly selected Japanese patients with LTG, 92 with POAG, and 99 normal subjects. The patients had all been diagnosed and followed up

in our clinic. Patients with LTG had glaucomatous optic disc cupping and visual field defects in at least one eye, and the intraocular pressures (IOPs) remained lower than 21 mmHg on repeated measurements; they had no history of retrobulbar neuritis, anterior ischaemic optic neuropathy, or intracranial lesion. Patients with POAG had glaucomatous optic disc cupping and visual field defects, and an IOP of 21 mmHg or more. Normal subjects, who were selected from patients in our clinic, had no abnormal ocular findings except refractive error in both eyes.

To compare the prevalence of migraine in Japanese patients with LTG and POAG with the results of Phelps and Corbett,³ the same questionnaire as Phelps and Corbett used was applied in the present study. Nearly all the subjects filled out the questionnaire by themselves in the waiting room in our clinic, but to some it was sent by mail because of difficulty in visiting. The questionnaire was filled up by 85% of patients with LTG, 79% of patients with POAG, and 76% of normal subjects (response rate). Informed consent was obtained from each subject after explanation of the purpose of the study. A headache which had three migrainous features (unilateral headache or ocular pain; nausea, vomiting; visual disturbance before headache) was defined as 'classical migraine'; a headache which had two migrainous features or more as 'probable migraine'; and a headache which had only one migrainous feature or more as 'possible migraine'. Student's *t* test and the χ^2 test were used for the statistical analysis, and the statistically significant level was taken as $p < 0.05$.

Results

The questionnaire was completed by a total of 225 subjects, including 77 patients with LTG, 73 patients with POAG, and 75 normal subjects. The mean age of the subjects was 58.2 (SD 13.7) years, and the male to female ratio was 108:117. The prevalence of headache in each of these three groups is summarised in Table 1, and the distribution of age and sex in each group is shown in Table 2. The mean age of each of the three groups showed no statistically significant difference ($p > 0.05$). The distributions by sex in the three groups were identical. The prevalence of headache with or without migrainous features (headache overall) was 51% (39/77) in patients with LTG, 42% (31/73) in patients with POAG, and 44% (33/75) in normal subjects, respectively. Classical migraine which had three migrainous features was observed in four of the 77 patients with LTG (5%), in two of the 73 patients with POAG (3%), and in two of the 75 normal subjects (3%). There was no statistically significant difference between these three groups

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($p > 0.05$). Probable migraine which had two migrainous features or more was observed in 13 of the 77 patients with LTG (17%), in eight of the 73 patients with POAG (11%), and in nine of the 75 normal subjects (12%). Although the prevalence of probable migraine was highest in the patients with LTG, no statistically difference was observed between the three groups ($p > 0.05$). And there was no significant difference in the prevalence of possible migraine or headache overall between the groups ($p > 0.05$).

Table 3 shows the prevalence of headache with regard to age and sex. The prevalence of headache in patients with LTG was somewhat higher than those in other subjects of either sex. However, no statistically significant difference in the prevalence of headache was found between the three groups ($p > 0.05$).

Following the questionnaire we reviewed the four patients with LTG who had a history of classical migraine. We found that two of them had misunderstood the questionnaire, for one patient had confused scintillating scotoma with photopsia or myodesopsia and the other had nausea or vomiting unrelated to headache. In only two of four patients with LTG was classical migraine strongly suspected. We also reviewed the two patients with POAG and two normal subjects who had three migrainous features; one normal subject had misunderstood the questionnaire.

Discussion

Migraine is characterised by recurrent, periodic headaches which are commonly unilateral and are usually associated with visual prodromata, nausea, vomiting, and other focal neurological symptoms, including numbness and tingling of the lips, face, and hands, slight confusion of thinking, weakness of an arm or leg, mild aphasia, dizziness, and uncertainty of gait, or drowsiness.⁷ The visual symptoms are probably related to ischaemia in the occipital cortex.⁸ The prevalence of migraine is reported to be approximately 10% of the population.⁹

Corbett *et al*⁴ found that 12 of 27 patients (44%) with LTG had a history of common or classical migraine. According to their case control study, which included the administration of a headache questionnaire,³ a higher prevalence of headache with or without features of migraine was found in patients with LTG than in patients with POAG, ocular hypertension, and normal controls. They therefore considered there were close aetiological and therapeutic connections between LTG and migraine.

Our results are shown to compare with those of Phelps and Corbett in Tables 4, 5, and 6. In our Japanese patients with LTG, POAG, and normal subjects the prevalence of headache with or without migrainous features (headache overall) and headache with two migrainous features or more (probable migraine) were lower than those in Phelps and Corbett's series (Tables 4 and 5). On the other hand the prevalence of cases with three migrainous features (classical migraine) was almost the same in our study and theirs (Table 6). Although in Phelps and Corbett's series, there was a statistically significant dif-

Table 1 Prevalence of headache (total)

	Classical migraine	Probable migraine	Possible migraine	Headache overall
LTG (n=77)	4 (5%)	13 (17%)	28 (36%)	39 (51%)
POAG (n=73)	2 (3%)	8 (11%)	23 (32%)	31 (42%)
Normal (n=75)	2 (3%)	9 (12%)	20 (27%)	33 (44%)

Table 2 Distribution by age and sex

Age	LTG (male:female)	POAG	Normal
30-39	9 (5:4)	10 (6:4)	11 (4:7)
40-49	10 (4:6)	10 (6:4)	12 (6:6)
50-59	18 (8:10)	16 (8:8)	14 (6:8)
60-69	20 (10:10)	19 (9:10)	20 (10:10)
70-79	20 (10:10)	18 (8:10)	18 (8:10)
Total	77 (37:40)	73 (37:36)	75 (34:41)
Mean	58.7 (SD 13.4)	58.3 (SD 13.5)	57.6 (SD 14.2)

Table 3 Prevalence of headache

Age	Male			Female		
	LTG	POAG	Normal	LTG	POAG	Normal
30-39	3/5	4/6	1/4	3/4	2/4	5/7
40-49	2/4	2/6	3/6	4/6	3/4	4/6
50-59	3/8	4/8	3/6	5/10	4/8	4/8
60-69	4/10	2/9	3/10	6/10	3/10	4/10
70-79	5/10	3/8	2/8	4/10	4/10	4/10
Total	17/37 (46%)	15/37 (41%)	12/34 (35%)	22/40 (55%)	16/36 (44%)	21/41 (51%)

Table 4 Prevalence of headache overall

	Our clinic	Phelps and Corbett ¹
LTG	39/77 (51%)	47/54 (87%)
POAG	31/73 (42%)	124/182 (68%)
Normal	33/75 (44%)	396/493 (80%)

Table 5 Prevalence of probable migraine

	Our clinic	Phelps and Corbett ¹
LTG	13/77 (17%)	16/54 (30%)
POAG	8/73 (11%)	33/182 (18%)
Normal	9/75 (12%)	96/493 (19%)

Table 6 Prevalence of classical migraine

	Our clinic	Phelps and Corbett ¹
LTG	4/77 (5%)	4/54 (7%)
POAG	2/73 (3%)	10/182 (5%)
Normal	2/75 (3%)	14/493 (3%)

ference between LTG and POAG in the prevalence of headache overall, in our series of Japanese patients there was no such difference between the three groups of patients (Tables 4, 5, and 6).

There are several possible reasons for the differences in prevalence of headache between our series and that of Phelps and Corbett, including racial differences and differences in the distribution by age and sex. Although a questionnaire seems to be a relatively objective method of determining prevalence of headache, the results may be influenced by whether each

patient could understand the questions clearly. In fact a thorough review of the patients suspected of classical migraine from their responses to the questionnaire revealed that only two had classical migraine. Thus its prevalence in LTG was found to be very low, 3% (2/77).

Our study did not show any significant relationship between migraine and LTG or POAG, and suggested that the patient's angiospastic state may have no implications for optic nerve damage in either LTG or POAG.

- 1 Chumbley LC, Brubaker RF. Low-tension glaucoma. *Am J Ophthalmol* 1976; 81: 761-7.
- 2 Drance SM, Sweeney VP, Morgan RW, Feldman F. Studies of factors involved in the production of low tension glaucoma. *Arch Ophthalmol* 1973; 89: 457-65.
- 3 Phelps CD, Corbett JJ. Migraine and low-tension glaucoma: a case-control study. *Invest Ophthalmol Vis Sci* 1985; 26: 1105-8.
- 4 Corbett JJ, Phelps CD, Eslinger P, Montague PR. The neurologic evaluation of patients with low-tension glaucoma. *Invest Ophthalmol Vis Sci* 1985; 26: 1101-5.
- 5 Drance SM. The neurologic evaluation of patients with low-tension glaucoma, comment. *Surv Ophthalmol* 1986; 31: 74-5.
- 6 Ederer F. Migraine and low-tension glaucoma. *Invest Ophthalmol Vis Sci* 1986; 27: 632-3.
- 7 Adams RD, Victor M. Headache and other craniofacial pains. *Principles of neurology*. 4th ed. New York: McGraw-Hill, 1989: chapter 9: 134.
- 8 Ziegler DK, Friedman AP. Migraine. *Merritt's textbook of neurology*. 8th ed. Philadelphia, London: Lea and Febiger, chapter 20, 1989: 773.
- 9 Troost BD. Migraine. *Clinical ophthalmology*. Philadelphia: Harper and Row, 1983; 2: chapter 19.

Cutting the cost of cataract surgery – a financial audit

J Filer, T J Roberts-Harry, J D Jagger

Abstract

We have analysed the cost of disposable equipment used during cataract surgery by eight different surgeons over a six-month period in the same hospital. By comparing the costs of single-use items used by each surgeon we highlight how significant savings can be made by change of technique (without an adverse effect on surgical outcome).

There is great emphasis on fiscal efficiency and making the National Health Service more cost effective. Cataract extraction with intraocular lens implantation is the commonest ophthalmic operation, and by costing the disposal items used by eight different surgeons at the same hospital we demonstrate how major savings may be made by modifying the amount and type of equipment used during surgery. This study is confined to

the cost of disposable equipment alone and we have made no effort to estimate the cost of non-disposable equipment, as the initial cost, depreciation, or revenue consequences in terms of maintenance and sterilisation was much more difficult to establish. Neither have we costed the theatre charge or complete episode of cataract extraction plus IOL from initial consultation to discharge.

We studied the cost involved for eight different surgeons operating at the Royal Free Hospital on uncomplicated extracapsular cataract extraction with intraocular lens implantation over a six-month period. There has not been a noticeable difference in clinical outcome, and the low incidences of postoperative complications have been broadly comparable. This is the subject of a future study.

Methods and results

The eight surgeons were divided into two groups. Group 1 were those who used automated cortical lens aspiration, and Group 2 were those who used manual cortical clean-up. Both groups used a different core of identical disposable equipment, and each surgeon had additional equipment depending on his or her preference. The core equipment in each of groups 1 and 2 is shown in Table 1. Table 2 shows the additional equipment used by each individual surgeon. It is thus possible to add together the automated or non-automated core to each individual's additional equipment price to give a total price per surgeon – Table 3.

The number of cataract extractions performed each month can be broken down into those individually for the eight different surgeons or taken as a whole. The number of cataract extractions per group and per surgeon over a six-month period is indicated in Table 4. The cost of disposal equipment on an individual and collective basis for each month and over the whole six-month period is shown in Table 5.

Discussion

The cost in terms of disposable equipment from surgeon to surgeon varies from £21.74 to £112.58. The average actual cost of performing 365 cataract extractions over the six-month period was £51.67 per case. If the least expensive surgeon had performed all the cataracts during this period and the figures projected for a 12-month period, the total cost would have been £15 870.20. If on the other hand the most expensive surgeon had performed the same number of cataract extractions over the same period, the cost would have been £82 344.00 – a difference of £66 313.20. If all eight surgeons had changed to adopt the disposable equipment of surgeon 5, the department would save

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Table 1 Core equipment

Equipment	Core 1	Core 2	Cost per item (£)
Viscoelastic agent	+		46.02
Automated aspiration Interkit	+		34.00
Balanced salt solution (20 ml)	+		2.15
Beaver micro blade	+	+	1.81
Ringer's solution (500 ml) +0.5 m adrenaline 1:100	+	+	1.37
Intravenous giving set		+	0.85
A60 extension set		+	0.84
Rycroft cannula	+	+	0.79
Lacrimal cannula	+	+	0.72
Irrigating cystotome	+		0.54
Jelonet 10×10	+		0.18
Cartella	+	+	0.12
Eye pad	+	+	0.10
Syringe×2 (2 ml)	+	+	0.06
Syringe×1 (5 ml)		+	0.05
Discardapad	+	+	0.05
Total cost per core	£87.91	£06.76	

Table 2 Additional equipment

Equipment	Cost per item (£)	Surgeon							
		1	2	3	4	5	6	7	8
Viscoelastic agent	46.02				+				+
Coaxial cannula	9.20						+	+	+
Miocol	7.44	+	+	+					
Nylon Alcon	6.50		+	+	+		+	+	+
Steridrape 1060	5.37		+	+	+	+		+	+
Nylon W1770	5.01	+				+			
Ethibond W883	3.78			+					
Silk W606	2.45	+							
Steridrape 1040	2.26						+		
Steridrape 1020	2.18	+							
Balanced salt solution (20 ml)	2.15					+			
Marcaine 0.5%	1.52	+							
Irrigating vectis	2.16				+	+		+	
Beaver blade	1.15		+	+	+				+
Silk W501	0.51		+		+				+
Subconjunctival injection (i)	0.43	+		+					+
Subconjunctival injection (ii)	0.28							+	
Monojet needle	0.25					+			
Jelonet 10×10	0.18								+
Syringe×1 (1 ml)	0.07						+		
Syringe×1 (10 ml)	0.06				+		+	+	
Melolin 5×5	0.04					+	+	+	
Blade no. 15	0.03	+							
Cost per surgeon		19.06	20.97	24.67	25.45	14.98	18.31	23.79	71.55

Table 3 Total cost per surgeon of disposable equipment

Surgeon	Cost per cataract (£)
3	112.58
2	108.88
1	106.97
8	78.31
4	32.21
7	30.55
6	25.07
5	21.74

Table 4 Cataract extractions performed over a six-month period expressed on an individual and collective basis

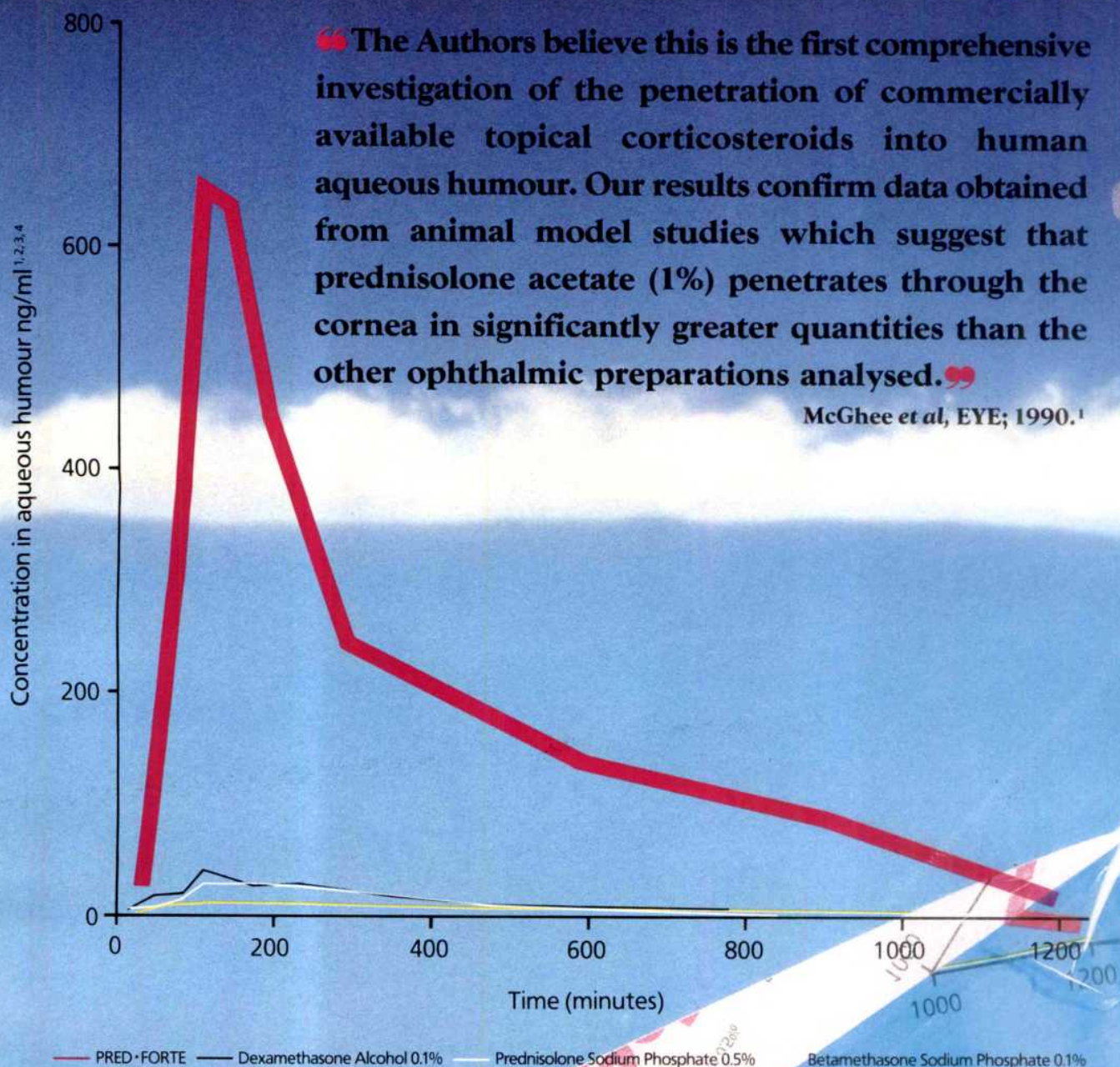
Surgeon	Month						Total
	1	2	3	4	5	6	
1	5	10	6	10	7	9	47
2	5	2	10	2	11	6	36
3	1	2	2	2	0	1	8
4	9	15	11	17	7	5	64
5	5	5	3	11	10	11	45
6	9	12	5	13	6	12	57
7	9	20	16	11	10	16	82
8	8	3	5	5	0	5	26
Total	51	69	58	71	51	65	365

Table 5 Cost of disposable equipment (£) over a six-month period expressed on an individual and collective basis

Surgeon	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Total
1	543.85	1069.70	641.82	1069.70	748.79	962.73	5027.59
2	544.40	217.76	1088.80	217.76	1197.68	653.28	3919.68
3	112.58	225.16	225.16	225.16	0.00	112.58	900.64
4	289.89	483.15	354.31	547.51	225.47	161.05	2061.38
5	108.70	108.70	65.22	239.14	217.40	239.14	978.30
6	225.63	300.84	125.35	325.91	150.42	300.84	1428.99
7	274.95	611.00	488.80	336.05	305.50	488.80	2505.10
8	626.48	234.93	391.55	391.55	0.00	391.55	2036.06
Total	2717.48	3251.24	3381.01	3352.78	2845.26	3309.97	18857.74

£21 862.94 per year, whereas annual expenditure at present on disposable equipment is £37 733.14.

We fully accept that it would be entirely wrong to impose the cheapest alternative on all surgeons and are fully cognisant that different techniques, training experience, and possible long-term outcome have not been accurately assessed. Surgeons may feel that more expensive equipment may be superior in quality and improve the long-term outcome, with a lower risk of complications. We have illustrated that by careful assessment of the costs of the alternative equipment major savings may be made in those areas where surgeons may feel that there is more than one alternative. Moreover it may be possible to modify one's technique with a reduction in cost without the patient's being adversely affected. However, it is only by long term assessment of surgical quality and its relationship to cost that resources may not be squandered. Certainly today there is a greatly increased awareness of medical audit, departmental budgets, and overall cost effectiveness, enabling money to be better spent on patient care.



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McGhee et al, EYE; 1990.¹

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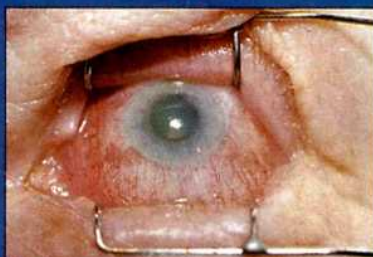
References 1. Penetration of Synthetic Corticosteroids into Human Aqueous Humour. McGhee C.N.J., Watson D.G., Midgley J., Noble M.J., Dutton G.N., Fern A.J. Eye 1990; 4: 526-530. 2. Penetration of Topically Applied Dexamethasone Alcohol into Human Aqueous Humour. Watson D.J., Noble M.J., Dutton G.N., Midgley J., Healey T., Arch Ophthalmol 1986; May 1988; 686-687. 3. Comparative Studies of the Penetration of Synthetic Corticosteroids into the Human Eye by GC-NIMS. Midgley J.M., McGhee C.N.J., Watson D.G., Dutton G.N., Fern A.J., Healey T., Arch Ophthalmol 1988 Dec; 4(Suppl): 16P. 4. Penetration of Topically Applied Prednisolone Sodium Phosphate into Human Aqueous Humour. McGhee C.N.J., Noble M.J., Watson D.G., Dutton G.N., Fern A.J., Healey T., Midgley J.M., Eye 1989; 3: 463-467.

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Influence of genotype on the natural history of untreated proliferative sickle retinopathy – an angiographic study

Peter D Fox, S J Rupert Vessey, Mark L Forshaw, Graham R Serjeant

Abstract

The natural history of untreated proliferative sickle retinopathy (PSR) has been observed in 35 patients (40 eyes) with homozygous sickle cell (SS) disease and in 112 patients (114 eyes) with sickle cell-haemoglobin C (SC) disease over a mean follow-up period of 4.5 years (range 0.5–14.0 years). In both genotypes progression of PSR was most frequent between ages 20 and 39 years. Spontaneous regression was more common in SS disease ($p=0.01$), and more likely to proceed to complete non-perfusion. In SC disease PSR tended to be stable in patients aged 40 and over, and non-perfused PSR lesions were significantly more likely to reperfuse ($p=0.01$) than in SS disease. In both genotypes regression was not influenced by size or elevation of the PSR lesion. The tendency for PSR to regress in SS disease suggests that treatment is unnecessary in SS patients aged 40 and over.

Vaso-occlusion in sickle cell disease induces peripheral retinal ischaemia with the subsequent risk of proliferative sickle retinopathy (PSR).^{1,2} This complication may cause visual loss from vitreous haemorrhage or retinal detachment¹ but may also resolve spontaneously.^{3,4} Since the natural history of PSR lesions is so variable, a knowledge of the determinants of progression and regression of PSR lesions is important both in the assessment of the efficacy of treatment and in the selection of patients most likely to benefit from treatment. The present study therefore addresses the natural history of untreated PSR lesions and examines the determinants of their outcome.

Patients and methods

The patients attended the Sickle Cell Clinic of the University of the West Indies between August 1970 and April 1989. The study was restricted to patients with homozygous sickle cell (SS) disease or sickle cell-haemoglobin C (SC) disease with perfused PSR on initial examination, and who had at least two angiographic assessments six months or more apart. Patients had either been randomised to control groups in treatment trials or had declined to enter the trials.

There were 40 eligible eyes in 35 SS patients (16 male, 19 female) and 114 eyes in 112 SC patients (59 male, 53 female). The mean age at initial fluorescein angiogram was 38 years (range 18–59 years) in SS disease and 30 years (range 15–58 years) in SC disease. Mean follow-up was

4.5 years (range 0.5–14.0 years) and did not differ between genotypes. Follow-up was terminated prematurely by vitreous haemorrhage in seven eyes (one SS, six SC), retinal detachment in four SC eyes, YAG vitreous membranolysis in one SC eye, and argon laser treatment of a retinal hole adjacent to a PSR lesion in one SC eye.

The characteristics of PSR lesions (number, flat or elevated, circumferential involvement) were documented on the initial angiogram, and subsequent angiograms were examined for evidence of progression, regression, or stability. Progression and regression were defined respectively as an increase or decrease in the number of PSR lesions in an eye or as an increase or decrease in the size of the capillary network of the neovascular tissue. Angiograms were assessed by the authors in a masked fashion.

The effect of age on behaviour of PSR lesions was examined by categorising the overall changes for each eye within the decades 10–19 years, 20–29 years, 30–39 years, and 40 years and above. Since some eyes contributed observations to more than one decade, the number of observations exceeded the number of eyes.

The role of haematological factors was assessed by examining these in patients with simple progression or regression. This examination was confined to patients with SC disease where an adequate number of eyes were available. Haematological indices included total haemoglobin (Hb), mean cell haemoglobin concentration (MCHC), mean cell volume (MCV), reticulocyte count (retics), fetal haemoglobin (HbF), and platelets. Hb, MCV, and platelet count were measured in a Coulter S plus IV haematology analyser. MCHC was derived from the spun microhaematocrit, reticulocytes were counted after staining with 5% brilliant cresyl blue for 30 minutes at 37°C, and HbF was measured by alkali denaturation.⁵ Multiple values for these indices were usually available in each patient, so the steady state values closest in time to the observations of PSR progression or regression were used in the analysis, and differences were assessed by the Mann-Whitney non-parametric test.

Results

At initial assessment there were 109 PSR lesions in 40 SS eyes (mean 2.7 lesions/eye) and 372 PSR lesions in 114 SC eyes (mean 3.3 lesions/eye). The great majority of these lesions (91% in SS eyes, 81% in SC eyes) subtended less than 15° of the circumference, and the mean circumferential involvement of perfused PSR at initial assess-

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Table 1 Overall change of proliferative sickle retinopathy according to age and genotype

Age group (years)	SS Disease				SC Disease			
	Number of eyes	Progress n (%)	Regress n (%)	Stable n (%)	Number of eyes	Progress n (%)	Regress n (%)	Stable n (%)
10-19	1	0	1	0	10	4 (40)	3 (30)	3 (30)
20-29	8	2 (25)	3 (38)	3 (38)	47	28 (60)	8 (17)	11 (23)
30-39	16	4 (25)	4 (25)	8 (50)	56	24 (43)	15 (27)	17 (30)
40+	22	3 (14)	9 (41)	10 (45)	24	7 (29)	1 (4)	16 (67)

ment was 30° in SS eyes and 40° in SC eyes. The subsequent changes by genotype and by age group within genotypes are summarised in Table 1. Analysis of changes within each genotype revealed no sex difference.

Progression of proliferative disease in both SS and SC disease was maximal in the 20-29 and 30-39 year age groups. There was no genotype or sex difference in progression.

Regression of PSR was significantly commoner in SS disease, occurring in 16/40 (40%) SS eyes compared with 23/114 (20%) SC eyes ($z=2.5$, $p=0.01$). Further analysis within age groups confirmed that the genotype difference was predominantly in patients aged 40 years and over ($z=3.0$, $p=0.002$). Regression leading to complete non-perfusion of all PSR lesions occurred in 8/40 (20%) SS eyes and in 8/114 (7%) SC eyes, this difference being significant ($z=2.3$, $p=0.02$). The mean age at diagnosis of complete non-perfusion was 29 years in SC disease and 41 years in SS disease. Patients proceeding to complete non-perfusion generally had fewer PSR lesions and below average initial circumferential involvement (20° in SS, 30° in SC disease).

Spontaneous non-perfusion of individual PSR lesions was commoner in SS disease ($z=2.3$, $p=0.02$) but was not significantly affected by size or elevation of the PSR lesion (Table 2). Reperfusion of previously non-perfused PSR lesions was significantly commoner in SC disease ($z=2.5$, $p=0.01$) and was usually observed within six months.

Comparison of haematological indices in 33 SC patients with progression and the 17 with regression revealed no significant differences.

Discussion

The abnormal vessel systems associated with proliferative sickle retinopathy may lead to visual loss by either vitreous haemorrhage or retinal detachment. There have therefore been many attempts to close these abnormal vessel systems by treatment,⁶⁻¹³ but such therapies may also produce potentially serious complications such as vitreous haemorrhage, retinal tears,¹³

choroidal neovascularisation,^{14,15} and retinal detachment. Furthermore, although PSR is common, especially in SC disease,¹⁶ visual loss is relatively infrequent.¹⁷ One explanation for these apparently conflicting observations is spontaneous non-perfusion of PSR lesions^{3,15,18} rendering them avascular and less prone to sight threatening complications.

The evidence from long term follow-up of PSR affected patients suggests that only a small proportion sustain complications resulting in visual loss, whereas the majority of PSR lesions either stabilise or undergo spontaneous non-perfusion with advancing age. Thus in the present study visual loss from vitreous haemorrhage or retinal detachment occurred in only 10/114 (9%) SC eyes monitored over a mean period of 4.5 years. While such visual loss is of some consequence, the relatively small proportion of eyes affected and the complications of therapy directed at rendering PSR lesions avascular indicate a need for greater knowledge of the natural history of PSR lesions. If the determinants of poor visual outcome could be understood, therapy could be directed towards this high risk group, leaving lower risk patients to undergo spontaneous non-perfusion.

The present study has examined the role of genotype, age, sex, and certain haematological indices as risk factors for spontaneous non-perfusion and had identified the SS genotype and age 40 years and over in SS disease as associates. However, the lack of haematological relationships with spontaneous non-perfusion in SC disease suggests that haematological indices have only a minor, or no, role in the development of non-perfusion. More studies are needed to clarify the determinants of the final visual outcome of proliferative sickle retinopathy, but the frequency of spontaneous regression in SS disease suggests that treatment in such patients aged 40 years and over is unnecessary.

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- Goldberg MF. Natural history of untreated proliferative sickle retinopathy. *Arch Ophthalmol* 1971; 85: 428-37.
- Condon PI, Serjeant GR. Progression of sickle cell eye disease in Jamaica. *Doc Ophthalmol* 1975; 39: 203-10.
- Nagpal KC, Patrianakos D, Asdourian GK, et al. Spontaneous regression (autoinfarction) of proliferative sickle retinopathy. *Am J Ophthalmol* 1975; 80: 885-92.
- Condon PI, Serjeant GR. Ocular findings in hemoglobin SC disease in Jamaica. *Am J Ophthalmol* 1972; 74: 921-31.
- Betke K, Marti HR, Schlicht I. Estimation of small percentages of foetal haemoglobin. *Nature* 1959; 184: 1877-8.
- Goldberg MF. Treatment of proliferative sickle retinopathy. *Ophthalmology* 1971; 75: 532-56.
- Goldberg MF, Acacio I. Argon laser photocoagulation of proliferative sickle retinopathy. *Arch Ophthalmol* 1973; 90: 35-44.
- Condon PI, Serjeant GR. Photocoagulation and diathermy in treatment of proliferative sickle retinopathy. *Br J Ophthalmol* 1974; 58: 650-62.
- Lee CB, Woolf MB, Galinos SO, et al. Cryotherapy of proliferative sickle retinopathy. Part I: Single freeze-thaw cycle. *Ann Ophthalmol* 1975; 7: 1299-308.
- Rednam KRV, Jampol LM, Goldberg MF. Scatter retinal photocoagulation for proliferative sickle retinopathy. *Am J Ophthalmol* 1982; 93: 594-9.
- Cruess AF, Stephens RF, Margargal LE, Brown GC. Peripheral circumferential retinal scatter photocoagulation for treatment of proliferative sickle retinopathy. *Ophthalmology* 1983; 90: 272-7.

Table 2 Spontaneous non-perfusion of individual PSR lesions according to size and genotype

Size of PSR	SS Disease			SC Disease		
	Total PSR eyes	Non-perfused PSR n (%)	Reperfused n (%)	Total PSR eyes	Non-perfused PSR n (%)	Reperfused n (%)
Small (0-14°)	99	31 (31)	1 (3)	303	66 (22)	15 (23)
Medium (15°-29°)	8	3 (38)	0	53	9 (17)	1
Large (≥30°)	2	0	0	16	2 (13)	1

- 12 Kimmel AS, Margargal LE, Stephens RF, Cruess AF. Peripheral circumferential retinal scatter photocoagulation for the treatment of proliferative sickle retinopathy. An update. *Ophthalmology* 1986; 93: 1429–34.
- 13 Jampol LM, Condon PI, Farber M, *et al.* A randomized clinical trial of feeder vessel photocoagulation of proliferative sickle retinopathy. I. Preliminary results. *Ophthalmology* 1983; 90: 540–5.
- 14 Galinos SO, Asdourian GK, Woolf MB, *et al.* Choroido-vitreal neovascularization after argon laser photocoagulation. *Arch Ophthalmol* 1975; 93: 524–30.
- 15 Condon PI, Jampol LM, Ford SM, Serjeant GR. Choroidal neovascularisation induced by photocoagulation in sickle cell disease. *Br J Ophthalmol* 1981; 65: 192–7.
- 16 Condon PI, Hayes RJ, Serjeant GR. Retinal and choroidal neovascularization in sickle cell disease. *Trans Ophthalmol Soc UK* 1980; 100: 434–9.
- 17 Moriarty BJ, Acheson RW, Condon PI, Serjeant GR. Patterns of visual loss in untreated sickle cell retinopathy. *Eye* 1988; 2: 330–5.
- 18 Condon PI, Serjeant GR. Behaviour of untreated proliferative sickle retinopathy. *Br J Ophthalmol* 1980; 64: 404–11.

Extraocular muscle surgery in myasthenia gravis

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Abstract

Myasthenia gravis is typically a disease of young people in active employment who need a field of binocular single vision. Although it is systemically controllable with a good chance of spontaneous remission, persistent loss of binocularity may cause chronic disability. We report our experience of extraocular muscle surgery in five patients with stable myasthenia gravis and persistent double vision. Extraocular muscle involvement was selective, giving rise to incomitant and concomitant squints, with individual muscle overactions as well as underactions. Treatment was by conventional recession and resection procedures with the additional use of Faden and adjustable sutures where appropriate. In all five cases a larger, stable field of binocular single vision was established. It is concluded that extraocular muscle surgery may be beneficial in selected cases of myasthenia gravis.

Myasthenia gravis (MG) is an autoimmune disorder characterised by a reduction in available post-synaptic acetylcholine receptors (AChR) on the endplates of neuromuscular junctions of skeletal muscle.¹ The symptoms of variable, fatiguable voluntary muscle weakness with spontaneous remissions and exacerbations are well known. In 75% of cases the initial presentation is with ptosis and/or diplopia, and over 90% develop ophthalmic symptoms at some stage in the course of the disease. Diagnosis is often delayed because ocular motility abnormalities may mimic other conditions and because no single test is always positive.² Young people with long life expectancies are commonly affected and ocular motility abnormalities causing disabling diplopia and loss of binocular single vision (BSV) may persist long after remission. Conventionally

this is managed by prisms or occlusion,³⁻⁶ but these measures may be poorly tolerated and leave unacceptable cosmetic results. In addition, loss of BSV may limit employment opportunities.

We report on five patients with stable systemic disease but in whom persistent unchanging diplopia left poor results. All benefited from extraocular muscle surgery.

Materials and methods

Five cases were identified from the records of the ocular motility clinics at the Western Ophthalmic Hospital and Moorfields Eye Hospital. All had a clinical diagnosis of MG confirmed by a positive edrophonium test and/or characteristic jitter phenomena on the electromyogram, together with the presence of anti-acetylcholine receptor antibodies. All were clinically and biochemically euthyroid, and cases with features suggesting coexisting dysthyroid ophthalmopathy were excluded. No cases had a thymic or other neoplasm, or evidence of connective tissue disease. All patients were symptomatically in disease remission but complained of troublesome, constant diplopia. None had clinically significant ptosis. After a minimum two-year period of stable orthoptic assessments and failure to tolerate prisms or monocular occlusion, extraocular muscle surgery was performed. All cases were followed up for a period of six months to six years after surgery. The clinical details are summarised on Tables 1 and 2.

Results

The cases are summarised on Table 3. Two are reported in detail.

CASE 1

In 1981 a fireman aged 22 years presented with variable fatiguable diplopia and limb and facial weakness. Following an equivocal response to intravenous edrophonium (Tensilon), generalised myasthenia gravis was diagnosed on the basis of positive titres for anticholinesterase receptor (AChR) antibodies and an electromyogram which showed muscle fibre fatigue on supramaximal nerve stimulation at 3-5 Hz. The systemic symptoms were controlled by thymectomy for thymic hyperplasia and oral pyridostigmine. However, troublesome horizontal diplopia persisted, and in 1983 he was referred for assessment.

The visual acuities and findings on intraocular examination were normal. There was a 3 mm ptosis on the right and mild bilateral orbicularis weakness. The prism cover test showed a V pattern exotropia of 6 dioptres on downgaze and 20 dioptres on elevation. Dissociated eye movement analysis (Fig 1A) indicated marked right

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Table 1 Diagnostic features

Patients					
No.	Sex	Age at presentation	Edrophonium	Anti-AChR antibodies	SFEMG
1	M	22	+	+	Normal
2	M	25	+	+	Normal
3	F	19	+	+	Normal
4	M	16	+	+	Abnormal
5	M	52	+	+	Normal

AChR=acetyl choline receptor. SFEMG=single fibre electromyogram.

Table 2 Systemic treatment

No. Patients	Anticholinesterases	Thymectomy	Immunosuppression (oral steroids)	Years stable
1	Yes	Yes	Yes	2
2	Yes	Yes	No	10
3	Yes	Yes	No	22
4	Yes	No	No	5
5	Yes	No	Yes	2

Table 3 Summary of ocular motility findings and surgical procedures

Patient	Eye movements	BSV field (degrees)	Operation	BSV field	Years stable follow-up
1	10 dioptre exotropia R: MR underaction L: LR overaction	30°	L: LR Faden	80	6
2	5-Dioptre left hypertropia 45-Dioptre exotropia L: MR underaction 10-Dioptre right hypertropia	Nil	(i) L: LR -6 MR +5 (ii) L: SO posterior tenotomy	40 50	2
3	60-Dioptre exotropia R: MR underaction 10-Dioptre left hypertropia	Nil	R: LR -9.5 MR + 10	30 with prisms	1
4	A pattern esotropia 55 dioptres upgaze 10 dioptres downgaze bilateral SO overaction bilateral IR underaction	Nil	(i) Bilateral MR -5 and SO posterior tenotomies (ii) Bilateral MR superposition	30 40	2 1
5	(1) 45-Dioptre exotropia right hypotropia ? IIIrd nerve palsy (2) Consecutive esotropia 30 dioptres R: LR underaction	Nil	(i) R: LR-, MR + (ii) R: LR +7 MR -2 (adj)	30	1

R=right, L=left. MR=medial rectus, LR=lateral rectus, IR=inferior rectus, SO=superior oblique. adj=adjustable suture. --=rectus recession (mm). +=rectus resection (mm). BSV=field of binocular single vision.

medial rectus underaction and left lateral rectus overaction. The field of binocular single vision (BSV) was reduced to 30° (Fig 1B).

After a 12-month period of observation the

motility abnormalities were unchanged and the systemic disease remained controlled. The patient was unable to tolerate prisms or occlusion and following a normal forced duction test

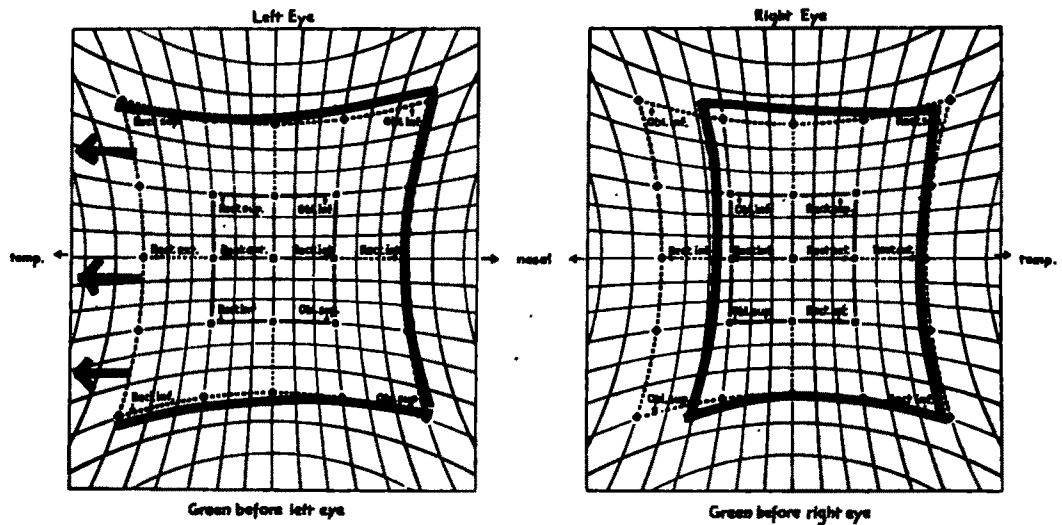


Figure 1A Hess chart showing exotropia with right medial rectus underaction and left lateral rectus overaction.

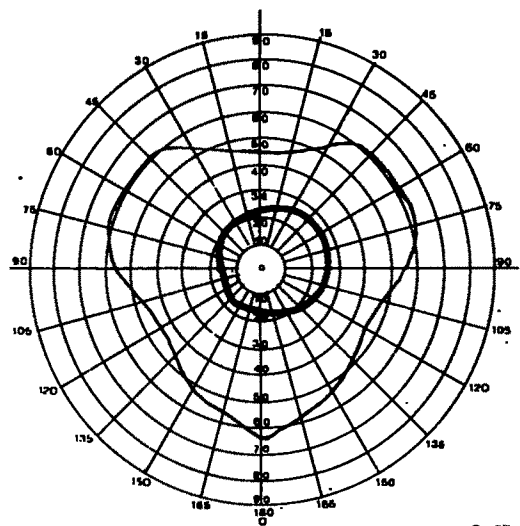


Figure 1B Field of binocular single vision before surgical treatment.

underwent a left lateral rectus Faden posterior fixation suture operation. The field of binocular single vision was increased to 80° arc (Fig 1C, D), and this improvement has been stable over six years of follow-up.

CASE 4
In 1984 a 16-year-old male college student developed diplopia, and a diagnosis of generalised myasthenia was made after detection of AChR antibodies and deltoid electromyographic abnormalities. Disease activity was controlled by oral prednisolone on alternate days, but a large angle convergent squint persisted.
In 1988 he was referred for assessment. This showed a large A pattern esotropia of 55 dioptres on downgaze and 10 dioptres on upgaze. Ocular movements showed marked bilateral superior oblique overactions and inferior rectus underactions (Fig 2A). There was no field of BSV.

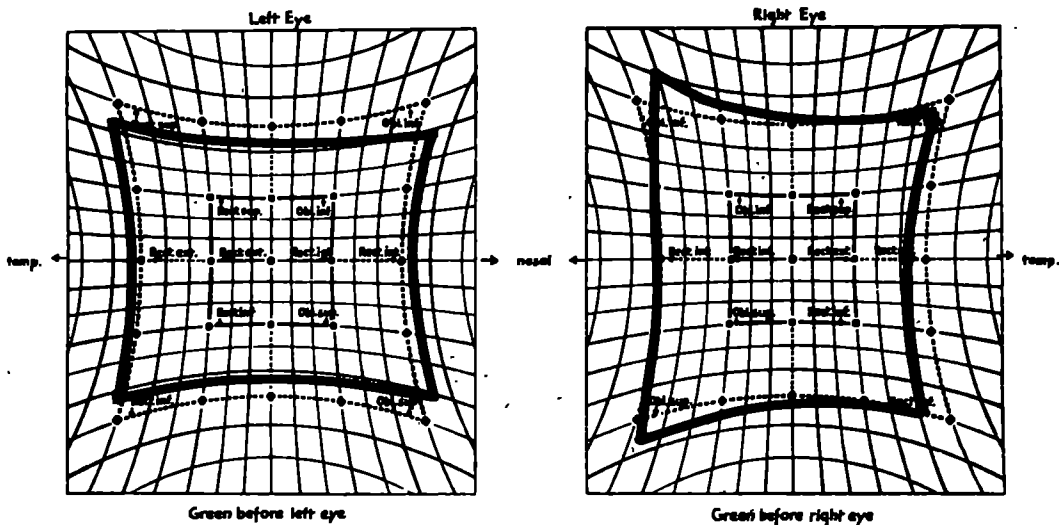


Figure 1C Hess chart after Faden procedure to left lateral rectus.

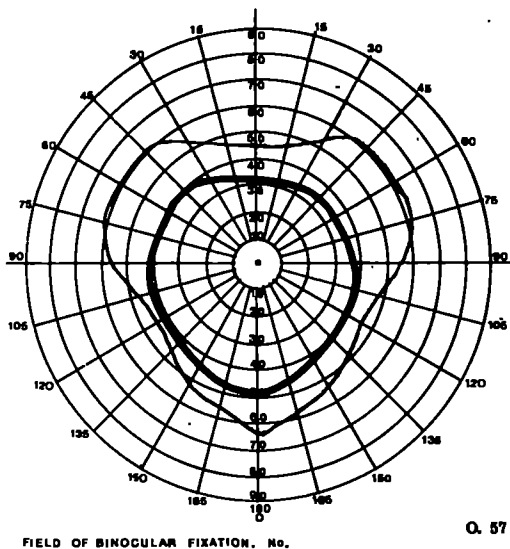


Figure 1D Field of binocular single vision after left lateral rectus Faden procedure.

half the muscle widths without further improvement. The clinical findings have remained stable for a further 12 months.

Discussion

Extraocular muscle surgery in myasthenia gravis is inappropriate in most cases, where both systemic and ocular manifestations may continue to show instability in spite of careful medical management.³⁻⁵ However, eventual remission is common among long-term survivors. In one follow-up study⁶ Oosterhuis found that of an original 58 patients 29 were still alive at 20 years; of these, 16 (55%) were in remission and the remaining 13 showed objective diminution of disease severity. A small subgroup of myasthenics appears to exist in whom such remission coexists with a stable squint which may limit rehabilitation opportunities. This is the category into which our five cases fit.

Over the next 12 months the strabismus remained unchanged, and his systemic disease was stable.

In January 1989 he underwent bilateral medial rectus recessions of 5 mm and bilateral superior oblique posterior 7/8 tenotomies. Postoperatively a BSV field of 30° was established, but the A pattern persisted with a 40 dioptres of esotropia on elevation and 5 dioptres on depression (Fig 2B). Six months later he underwent bilateral medial rectus insertion elevations by

Ocular motility analysis (Table 3 and Figs 1 and 2) shows that individual muscle involvement was highly selective and that secondary overactions were common. This clinical observation has not to our knowledge been previously described. However, electrophysiological and histological studies do support our observation of highly selective, variable involvement of muscles in myasthenia gravis.¹² Between one muscle and another the electromyogram may show variable

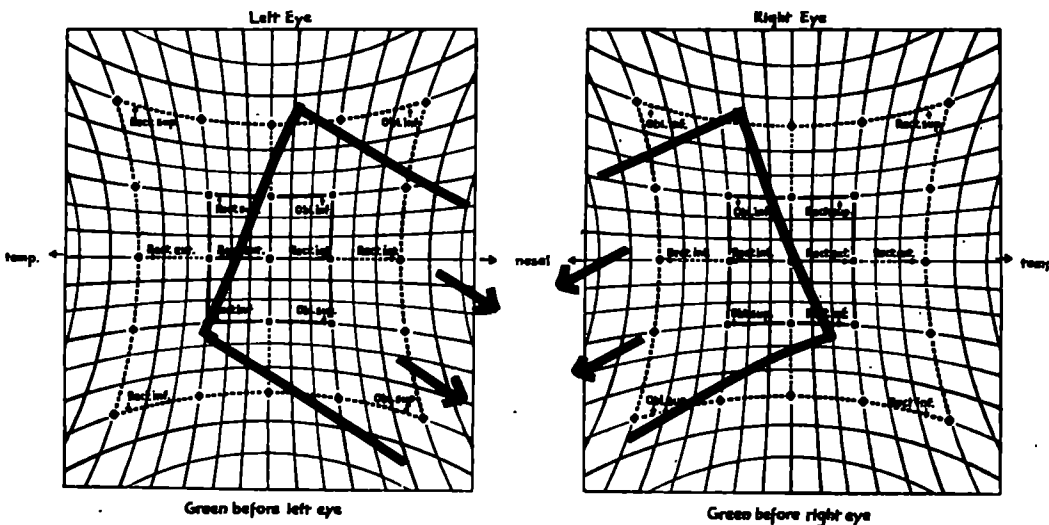


Figure 2A. Hess chart showing A pattern esotropia and bilateral superior oblique overactions.

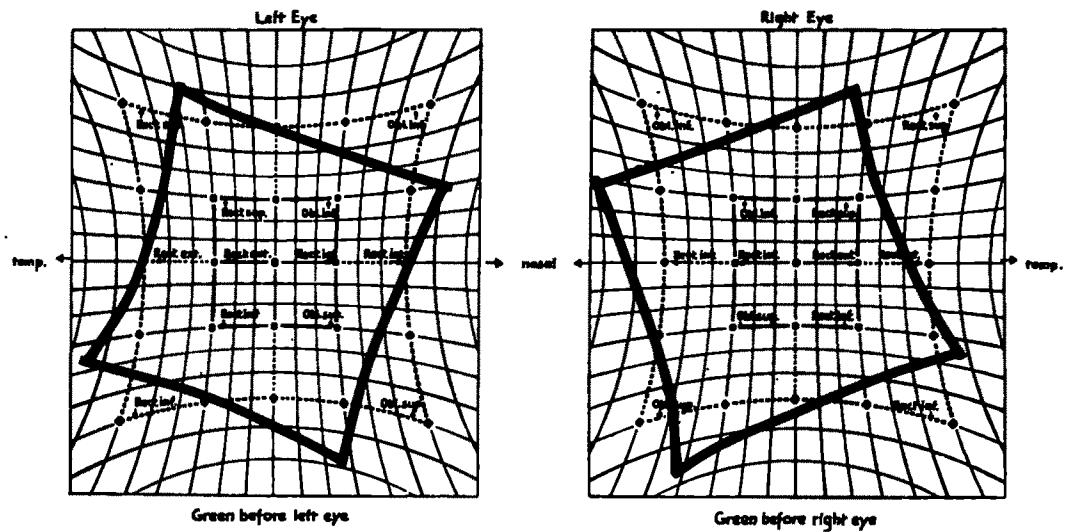


Figure 2B Hess chart after bilateral superior oblique posterior tenotomies.

abnormal decremental responses of the evoked compound muscle action potential on repetitive nerve stimulation. Within one muscle the single fibre EMG may show characteristic jitter phenomena arising from variations in activation time on the action potentials of two fibres from the same motor unit. Similar variability is shown in AChR receptor densities in histopathological studies in muscle biopsy specimens. For these reasons, we have avoided surgery on 'weak' underacting muscles where possible and have performed weakening procedures on overacting relatively healthy muscles. Cases 1 and 4 were managed solely by this approach. For example, in the concomitant pattern seen in case 4 rectus muscle recession and transposition and superior oblique tenotomy were appropriate,⁷ while in the incomitant cases the Faden posterior fixation and recession on an adjustable suture were preferred.⁸⁻¹¹ However, single rectus muscle resections were performed in cases 2, 3, and 5 with satisfactory results.

In conclusion, patients with a definite diagnosis of myasthenia gravis whose disease process is stable or in remission, but who continue to

suffer from disabling diplopia and loss of binocularity, may safely and effectively be managed by extraocular muscle surgery.

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- 1 Seybold ME. Myasthenia gravis: a clinical and basic science review. *JAMA* 1983; 250: 2516-21.
- 2 Oosterhuis HJGH. *Myasthenia gravis. Clinical neurology and neuro-surgery monographs*. Edinburgh: Churchill Livingstone, 1984: 5.
- 3 Mein J, Harcourt B. *Diagnosis and management of ocular motility disorders*. Oxford: Blackwell, 1986: chapter 19: 324.
- 4 Glaser JS. Infranuclear disorders of eye movement. In: Duane TD, Jaeger EA, eds. *Clinical ophthalmology*. Philadelphia: Lipincott, 1988; 2: chapter 12: 31-7.
- 5 Miller NR. Myopathies and disorders of neuro-muscular transmission. *Walsh and Hoyt's clinical neuro-ophthalmology*. 4th ed. St Louis: Mosby, 1987; 2: chapter 36: 859.
- 6 Oosterhuis HJGH. The natural course of myasthenia gravis: a long term follow-up study. *J Neurol Neurosurg Psychiatry* 1989; 52: 1121-7.
- 7 Willshaw HE, O'Connor GM. Transposition surgery in childhood strabismus. *Eye* 1988; 2: 41-3.
- 8 Scott AB. The Faden operation: mechanical effects. *Am Orthopt J* 1984; 27: 44-7.
- 9 Harcourt B. Faden operation (posterior fixation sutures). *Eye* 1988; 2: 36-40.
- 10 Rosenblum AL, Metz HS, Carlson M, Jampolsky AL. Adjustable rectus muscle recession surgery. *Arch Ophthalmol* 1977; 95: 817-20.
- 11 Fells P. The use of adjustable sutures. *Trans Ophthalmol Soc UK* 1981; 101: 279-83.

Optic nerve hypoplasia, encephalopathy, and neurodevelopmental handicap

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Abstract

Abnormalities of the central nervous system are frequently described in optic nerve hypoplasia. In a longitudinal study of 46 consecutive children (32 term, 14 preterm) with bilateral optic nerve hypoplasia 32 (69.5%) had associated neurodevelopmental handicap. Of these, 90% had structural central nervous system abnormalities on computed tomographic brain scans. Neurodevelopmental handicap occurred in 62.5% of the term and 86% of the preterm infants respectively. Term infants had a greater incidence of ventral developmental midline defects and proportionately fewer maternal and/or neonatal complications throughout pregnancy, while encephaloclastic lesions were commoner among the premature infants. An association of optic nerve hypoplasia with the twin transfusion syndrome and prenatal vascular encephalopathies is described.

Optic nerve hypoplasia is a non-progressive congenital abnormality of multifactorial aetiology. Its pathogenesis is not fully understood, but it may follow a variety of insults to any part of the developing visual pathways.¹⁻³ It is a major cause of visual loss in childhood and may be associated with important central nervous system and endocrine abnormalities,⁴⁻¹¹ which include septo-optic dysplasia, porencephaly, encephalocele, congenital suprasellar tumours, hypothyroidism, diabetes insipidus, growth hormone deficiency, and many others. These have recently been the subject of a minireview.¹² The increasing numbers of children described with this abnormality may reflect increased awareness on the part of ophthalmologists as well as an increase in its prevalence.

In contrast to some earlier reports, neurodevelopmental handicaps are being increasingly recognised in association with optic nerve hypoplasia, though their prevalence in and interrelationship with this anomaly have not been fully established. We serially assessed 46 cases of bilateral optic nerve hypoplasia, 32 of which had neurodevelopmental handicap. We examined the factors involved in the simultaneous occurrence of both conditions and describe the association of this anomaly with vascular encephalopathies, in particular the twin transfusion syndrome.¹³

Patients and methods

The study population consisted of 46 consecutive children with bilateral optic nerve hypoplasia who attended the Paediatric Ophthalmology Department of the Children's Hospital, Temple

Street, Dublin, from 1985 to 1989. Physical and neurological examinations showed that 32 children (18 males, 14 females) had variable degrees of neurodevelopmental handicap, of which mental retardation, cerebral palsy, and epilepsy were the commonest. The diagnosis of optic nerve hypoplasia was made or confirmed by two of us (MOK, RB) based on a combination of characteristic features. These included (1) a small optic nerve head, (2) a double pigmentary ring sign, and (3) an abnormal nerve fibre layer.¹⁴ Various objective means of confirming the diagnosis can be used,^{7,15} as the ophthalmoscopic diagnosis in milder cases may be difficult. However, these tests would have required greater patient co-operation than most children in this study could have provided.

Each child underwent a detailed ophthalmic examination. A history was obtained from the case records and from parents or guardians. This included gestational age, obstetric history, maternal medical history, and prenatal, perinatal, and postnatal complications. The referral pattern for each patient was documented. Visual acuity was estimated by ocular motor fixation patterns, forced choice preferential looking, and Sheridan and Gardiner or Snellen acuity testing. Appropriate tests were selected on the basis of the patient's age and level of co-operation.

Most of the children were examined by computed tomographic (CT) brain or magnetic resonance imaging scans, electroretinography and pattern stimulation, or diffuse light visual evoked responses. A paediatrician and/or paediatric neurologist examined each child before or within three months of their initial ophthalmic assessment.

Results

Children with optic nerve hypoplasia and neurodevelopmental handicap were divided into three groups. There were 12 children in group 1 (Table 1) with bilateral optic nerve hypoplasia and neurodevelopmental handicap who were born prematurely and 20 children in group 2 (Table 2) with bilateral optic nerve hypoplasia and neurodevelopmental handicap who were born at or after 37 weeks gestation. There were 14 children in group 3 with bilateral optic nerve hypoplasia who had no neurodevelopmental handicap.

All children in group 1 (Table 1) were born between the 26th and 33rd week, and when last seen their ages ranged from 9 to 56 months. All had been initially referred by paediatricians for visual assessment. Three had been delivered by emergency caesarian section, one for failure to progress in the second stage of labour and two for fetal distress. Four children were products of

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Table 1 Clinical findings in 12 children with bilateral optic nerve hypoplasia and neurodevelopmental handicap born prematurely (≤ 36 weeks gestation)

Patient/ gestational age (weeks)	Birth history	Pre- and perinatal history	CT or MRI diagnosis	Associated fundus findings
1/28	Assisted breech delivery	Severe RDS GMH-IVH	Porencephaly	—
2/26	SVD	Severe RDS GMH-IVH	CPVL	Regressed ROP
3/30	SVD	PET and APH	Diffuse cerebral and cerebellar atrophy	Atrophic discs
	TTS	Apnoea of prematurity		
4/30	CS	Severe RDS GMH-IVH	Suprasellar arachnoid cyst with hydrocephalus	—
5/32	SVD	Severe RDS	CPVL	Atrophic discs
	TTS		Diffuse cerebral atrophy	
6/30	SVD	Severe RDS GMH-IVH	CPVL	—
7/30	SVD twin	Severe RDS GMH-IVH	CPVL cerebral atrophy	—
8/30	CS	Maternal anaemia	CPVL cerebral atrophy	—
9/33	CS	Severe PET	Normal	—
10/27	SVD	RDS GMH-IVH	Diffuse cerebral atrophy	Regressed ROP
11/28	Placenta praevia	RDS GMH-IVH	—	Regressed ROP
12/27	SVD	RDS GMH-IVH	Diffuse cerebral atrophy	Regressed ROP

CT=computed tomographic brain scan. MRI=magnetic resonance imaging scan. RDS=respiratory distress syndrome. GMH-IVH=germinal matrix haemorrhage—intraventricular haemorrhage. ROP=retinopathy of prematurity. SVD=spontaneous vaginal delivery. CPVL=cystic periventricular leucomalacia. TTS=twin transfusion syndrome. PET=pre-eclampsic toxemia. APH=antepartum haemorrhage. CS=caesarian section. SLE=systemic lupus erythematosus.

twin pregnancies, and two of these suffered from twin transfusion syndrome. Maternal complications included severe pre-eclampsia in two cases, active systemic lupus erythematosus in one, and maternal anaemia of 7.5 g/dl in one mother who initially presented some days before going into spontaneous labour at 30 weeks gestation. There was no history of maternal diabetes mellitus. All 12 infants had a complicated perinatal/neonatal period.

Most recent visual acuities ranged from apparently normal to no visual fixation. The

amplitude of the binocular flash visual evoked potential correlated better with the visual acuity than did the latent interval.¹⁶ There were six cases with a visual acuity of $\leq 6/60$ (cases 2, 3, 8, 9, 10, 12), three cases with an acuity of $\geq 6/9$ (cases 1, 6, 7), and three (cases 4, 5, 11) with intermediate levels. Other ocular abnormalities observed were bilateral optic disc pallor in two cases, presumed cortical visual loss in three, and regressed retinopathy of prematurity in four.

All 12 children had cerebral ultrasound and/or computed tomographic brain (CT) scans performed. Periventricular haemorrhage was visible in six cases by ultrasonography in the neonatal period. One child (case 9) had a normal CT scan. The other 11 scans showed either diffuse cerebral atrophy and/or other encephaloclastic lesions of the developing brain (Table 2). The latter arise from the destruction of previously formed cerebral tissue by a vascular insult. There were no isolated anterior midline developmental defects.

There were 20 children in group 2 (Table 2). When they were last seen their ages ranged from 13 to 80 months. All were referred by paediatricians because of suspected visual handicap. There was no history of maternal diabetes mellitus. Eighteen births were uncomplicated. One mother with twins had an emergency forceps delivery for failure to progress in the second stage of labour (case 21), and one infant had perinatal asphyxia in association with meconium aspiration. Five infants had congenital hydrocephalus and one had cranial diabetes insipidus. An intrauterine infection was suspected in three children (cases 16, 24, 26), though unproved in two. The third had cytomegalovirus isolated from her urine three days postnatally (case 24). Eight infants had agenesis of the corpus callosum on CT scan. In addition, three of these had primary and one (case 18) had secondary microcephaly.

Visual acuities ranged from probably normal to no visual fixation. The amplitude of the binocular flash visual evoked potential correlated better with the visual acuities than the latent interval. There were three cases with acuities of $\geq 6/9$ (cases 15, 25, 26), one with an acuity of 6/12 (case 20), and the remainder with acuities of $\leq 6/60$. Seven cases had optic disc pallor in association with hypoplastic discs.

There were 14 children with no evidence of neurodevelopmental handicap when assessed (group 3). Three were born before 32 weeks and the remainder after 36 weeks gestation. There was no maternal history of diabetes mellitus or epilepsy. Two of the premature infants were initially referred by paediatricians for retinopathy of prematurity (ROP) screening. One had bilateral optic nerve hypoplasia in association with mild ROP, while the other, who was born to a mother with pre-eclampsic toxemia, had isolated optic nerve hypoplasia, and thin optic nerves were subsequently identified on CT scan. The third infant was referred at 5 months with early onset esotropia. Of the 11 children born after 36 weeks gestation five were referred by paediatricians with suspected visual handicap. The diagnoses of the referred patients included oculocutaneous albinism, fetal alcohol effects,

Table 2 Clinical findings in 20 children with bilateral optic nerve hypoplasia and neurodevelopmental handicap born at or after 37 weeks gestation

Patient no	Birth history	Pre- and perinatal complications	CT or MRI diagnosis	Associated fundus findings
13	SVD	—	Agenesis, corpus callosum	—
14	SVD	—	Agenesis, corpus callosum	—
15	SVD	—	Agenesis, corpus callosum	—
16	SVD	Suspected IUT infection	Agenesis, corpus callosum	—
17	SVD	—	Agenesis, corpus callosum, congenital hydrocephalus, diffuse cerebral atrophy	Atrophic discs
18	SVD	Postnatal encephalopathic illness	Agenesis, corpus callosum, diffuse cerebral atrophy	—
19	SVD	—	Agenesis, corpus callosum, Joubert's syndrome	Pigmentary retinopathy
20	SVD	—	Agenesis, corpus callosum	—
21	SVD twin	TTS HIE	Schizencephaly, diffuse cerebral atrophy	Atrophic discs
22	SVD	—	Aqueduct stenosis, hydrocephalus	Atrophic discs
23	SVD	Familial neurodegenerative disorder	Diffuse cerebral atrophy	Atrophic discs
24	SVD	Intrauterine CMV infection	Schizencephaly	Atrophic discs
25	SVD	—	Diffuse cerebral atrophy	—
26	SVD	—	Normal	Pigmentary retinopathy
27	SVD	—	Holoprosencephaly	—
28	SVD	—	Porencephaly, diffuse cerebral atrophy	Atrophic discs
29	SVD	—	Congenital hydrocephalus	—
30	SVD	—	Holoprosencephaly	Atrophic discs
31	SVD	Birth Asphyxia	Congenital hydrocephalus Dandy-Walker syndrome	—
32	SVD	—	Congenital hydrocephalus	—

CT=computed tomographic brain scan. MRI=magnetic resonance imaging scan. SVD=spontaneous vaginal delivery. IUT=intrauterine. TTS=twin transfusion syndrome. HIE=hypoxia ischaemic encephalopathy. CMV=cytomegalovirus.

dysmorphic syndrome, postencephalopathic illness, and nystagmus secondary to isolated optic nerve hypoplasia. Six children were referred by their family practitioner. Of these two had albinism, three presented with strabismus, and one had nystagmus, an alternating esotropia, bilateral optic nerve hypoplasia, and a normal CT scan. None of the 46 children studied had tumours of visual pathways.⁶

Discussion

Optic nerve hypoplasia is not a specific disease but a morphological diagnosis which may result from damage at any location in the developing visual pathways.¹⁷ Likewise the location of the injury to the developing brain, causing neurodevelopmental handicap, may vary in accordance with the time in utero when the fetus was exposed to the insult, while its sequelae may or may not be visible on CT scan. This may explain why intrauterine insults sufficient to produce neurodevelopmental handicap may also result in optic nerve hypoplasia.

Skarf and Hoyt¹⁸ noted that delayed development was the most frequently associated non-visual complication. Nineteen of 41 children (46%) with symmetrical bilateral optic nerve hypoplasia had developmental delay. Margalith *et al*¹⁹ noted neuropsychiatric handicaps in 72.6% of 51 patients (92% bilateral), of which mental retardation (70.6%) and cerebral palsy (56.9%) were the most frequent. Edwards and Layden²⁰ described a series of 14 cases of bilateral optic nerve hypoplasia of which seven had evidence of cerebral palsy and/or mental handicap. Neuroradiological abnormalities were detected in 61% of the 93 patients with bilateral optic nerve hypoplasia in these three series. The results differed from those of earlier studies, as Walton and Robb²¹ reported on 20 patients with optic nerve hypoplasia (12 bilateral) who enjoyed normal growth and development, while Acers²² commented on the infrequent association of optic nerve hypoplasia with mental and/or physical handicap among a series of 45 cases (40 bilateral). In our series 69.5% of 46 cases had neurodevelopmental handicap, and 90% of these had neuroradiological abnormalities. Our database was selective in that 40 of the 46 children were referred by paediatricians for screening or with suspected visual handicap.

It was possible to divide the neurodevelopmentally handicapped children into two groups on the basis of gestational age. There were 12 cases born prematurely and 20 born after 36 weeks gestation. We, like Margalith *et al*¹⁹ found the prevalence of perinatal/neonatal and maternal complications to be substantially higher among infants born prematurely. Four of the 12 premature children also had regressed retinopathy of prematurity and germinal matrix-intraventricular haemorrhages. Brown *et al*²³ observed a positive correlation between retinopathy of prematurity and intraventricular haemorrhage in premature infants, while others^{24,25} have suggested that severe retinopathy of prematurity and periventricular leucomalacia may both be associated with episodes of cerebrovascular insufficiency. We suggest that the simultaneous

occurrence of optic nerve hypoplasia in such patients may imply a contributory ischaemic basis for all three events. To our knowledge no study exists which examines the link, if any, between retinopathy of prematurity and optic nerve hypoplasia.

Ventral developmental midline defects occurred exclusively in the children born at or near term. These represent anomalies in closure of the anterior neural tube, and severe defects may be associated with epilepsy and mental/physical retardation of variable severity.²⁶ Seven of eight cases in this series with agenesis of the corpus callosum, optic nerve hypoplasia, and neurodevelopmental handicap were products of apparently normal pregnancies. The aetiology of optic nerve hypoplasia in a number of the other 12 cases was unknown (Table 2). One infant (case 24) had intrauterine cytomegalovirus infection. The significance of this association, which was previously reported by Hittner *et al*, is unclear.²⁷

Congenital hydrocephalus has been infrequently described in association with optic nerve hypoplasia.^{8,19,21,22} Ghose²⁸ did not describe any case in a series of 200 patients with hydrocephalus. We noted five children born at term with congenital hydrocephalus and optic nerve hypoplasia (four obstructive, one communicating). One of these had the Dandy-Walker syndrome, which is frequently associated with other central nervous system abnormalities. One must assume that either optic nerve hypoplasia predated and is unrelated to the hydrocephalus, or that optic nerve hypoplasia can result from this defect, occurring some time prior to the full development of the visual system.

Likewise the simultaneous occurrence of optic nerve hypoplasia and optic atrophy is being recognised with increasing frequency,^{1,8,19} while the difficulty in differentiating one from the other in some cases may be owing to an insult to the near completely developed visual pathways.¹ The fact that some believe that hypoplastic discs may be pale or normal in colour further confuses diagnostic interpretation in young children.²⁹ Margalith *et al*¹⁹ described 47 patients with bilateral optic nerve hypoplasia, 16% of whom had associated optic atrophy, while nine of 32 patients (28%) in this series had coexisting optic atrophy.

The pathogenesis of encephalopathy and encephaloclastic lesions in the developing brain is diverse and rarely demonstrable.^{2,17} Periventricular haemorrhage, which is usually preceded by cerebral ischaemia,³⁰ was identified in six of the 12 cases born prematurely. Functional disorders of perfusion such as ischaemia from placental abruption, toxemia (cases three and nine), or transient vasculitis (case 4) may play a part. Other postulated aetiologies include deficient maternal nutrition (case 8) and anomalies of placental development. To our knowledge the twin transfusion syndrome (cases 3, 5, 21) has not been previously described in association with optic nerve hypoplasia. It was Benirschke³¹ who first implicated the death of a monozygotic twin as a potential cause for problems in the surviving twin as a consequence of disseminated intravascular coagulation or from emboli from the

deceased cotwin entering the circulation of the survivor. Melnick³² subsequently stated that 1% of monozygotic twin births have severe brain defects as a consequence of the foregoing mechanisms. They and others¹³ described surviving infants with porencephaly and/or hydrancephaly who were usually severely mentally retarded with microcephaly, spastic diplegia, and seizures.

Optic nerve hypoplasia, particularly if bilateral, may be associated with a large variety of ocular and systemic abnormalities. The selection of patients referred to ophthalmic departments can undoubtedly lead to bias. However, the comparison of our findings with other published series allows further insight into the spectrum of optic nerve hypoplasia. Good visual acuity ($\geq 6/9$) was present in a minority (6 of 32) of children, while normal CT scans may be found in cases with visual, mental, and physical handicap, indicating the diverse and unpredictable findings that have come to be expected with this anomaly.³³ We confirmed the general impression that bilateral optic nerve hypoplasia is associated with neurodevelopmental handicap in a considerable percentage of affected term and preterm infants, while the occurrence of optic nerve hypoplasia and hypoxic-ischaemic brain injury in premature infants with or without associated retinopathy of prematurity may suggest common underlying links and merits further study. Similarly, the temporal relationship and significance of coexisting optic nerve hypoplasia and atrophy needs further elucidation.

All children with bilateral optic nerve hypoplasia, and in particular those with impaired vision and suspected neurodevelopmental handicap, should be considered for a CT brain scan and referral to a paediatrician for assessment of their developmental, general, and endocrinological status.

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- 1 Frisen L, Holmegaard L. Spectrum of optic nerve hypoplasia. *Br J Ophthalmol* 1978; 62: 7-15.
- 2 Mosier MA, Lieberman MF, Green R, Knox DL. Hypoplasia of the optic nerve. *Arch Ophthalmol* 1978; 96: 1437-42.
- 3 Fielder AR, Levene MI, Troughton JQ, Tanner MS. Optic nerve hypoplasia in infancy. *J R Soc Med* 1986; 79: 25-9.
- 4 Hoyt WF, Kaplan SL, Grumbach MM, Glaser JS. Septo-optic dysplasia and pituitary dwarfism. *Lancet* 1970; ii: 893-4.
- 5 Olivier R, Billson F. Optic nerve hypoplasia: a review. *J Child Neurol* 1986; 1: 181-8.
- 6 Taylor D. Congenital tumours of the anterior visual system with dysplasia of the optic discs. *Br J Ophthalmol* 1982; 66: 455-63.
- 7 Lambert SR, Hoyt CS, Narahara MH. Optic nerve hypoplasia. *Surv Ophthalmol* 1987; 32: 1-9.
- 8 Rogers GL, Brown D, Gray I, Bremer D. Bilateral optic nerve hypoplasia associated with cerebral atrophy. *J Pediatr Ophthalmol Strabismus* 1981; 18: 18-22.
- 9 Greenfield PS, Wilcox LM, Weiter J, Adelman L. Hypoplasia of the optic nerve in association with porencephaly. *J Pediatr Ophthalmol Strabismus* 1980; 17: 175-80.
- 10 Patel H, Tze WJ, Crichton JU, McCormick AQ, Robinson GC, Dolman CL. Optic nerve hypoplasia with hypopituitarism. *Am J Dis Child* 1975; 129: 175-80.
- 11 West J, Burke JP, Strachan I. Carbamazepine, epilepsy, and optic nerve hypoplasia. *Br J Ophthalmol* 1990; 74: 511.
- 12 Zeki SM, Dutton GN. Optic nerve hypoplasia in children. *Br J Ophthalmol* 1990; 74: 300-4.
- 13 Tan KL, Tan R, Tan SH, Tan AM. The twin transfusion syndrome. Clinical observations on 35 affected pairs. *Clin Pediatr (Phila)* 1979; 18: 111-4.
- 14 Apple DJ, Robb MF, Walsh PM. Congenital anomalies of the optic disc. *Surv Ophthalmol* 1982; 27: 3-41.
- 15 Alvarez E, Wakakura M, Khan Z, Dutton GN. The disc-macula distance to disc diameter ratio: a new test for confirming optic nerve hypoplasia in young children. *J Pediatr Ophthalmol Strabismus* 1988; 25: 151-4.
- 16 Sprague JB, Wilson WB. Electrophysiologic findings in bilateral optic nerve hypoplasia. *Arch Ophthalmol* 1981; 99: 1028-9.
- 17 Novakovic P, Taylor DS, Hoyt WF. Localising patterns of optic nerve hypoplasia. *Br J Ophthalmol* 1988; 72: 176-82.
- 18 Skarf B, Hoyt CS. Optic nerve hypoplasia in children. Association with anomalies of the endocrine and CNS. *Arch Ophthalmol* 1984; 102: 62-7.
- 19 Margalith D, Jan JB, McCormick AQ, Tze WJ, Lapointe J. Clinical spectrum of congenital optic nerve hypoplasia. Review of 51 patients. *Dev Med Child Neurol* 1984; 26: 311-22.
- 20 Edwards WC, Layden WE. Optic nerve hypoplasia. *Am J Ophthalmol* 1970; 70: 950-9.
- 21 Walton DS, Robb RM. Optic nerve hypoplasia. A report of 20 cases. *Arch Ophthalmol* 1970; 84: 572-8.
- 22 Acers TE. Optic nerve hypoplasia. Septo-optico-dysplasia syndrome. *Trans Am Ophthalmol Soc* 1981; 79: 429-57.
- 23 Brown DR, Milley JR, Riperti UZ, Biglan AW. Retinopathy of prematurity, risk factors in a five year cohort of critically ill premature infants. *Am J Dis Child* 1987; 141: 154-60.
- 24 Ng YK, Fielder AR, Levene MI, Troughton JQ, McLellan N. Are severe acute retinopathy of prematurity and severe periventricular leucomalacia both ischaemic insults? *Br J Ophthalmol* 1989; 73: 111-4.
- 25 Ng YK, Fielder AR, Shaw DE, Levene MI. Acute retinopathy of prematurity: risk factors. *Arch Dis Child* 1988; 63: 693-4.
- 26 Rakic P, Yakolev PI. Development of the corpus callosum and cavum septi in man. *J Diurnal Science* 1968; 132: 45-72.
- 27 Hittner HM, Desmond MM, Montgomery JR. Optic nerve manifestations of human congenital cytomegalovirus infection. *Am J Ophthalmol* 1976; 81: 661-5.
- 28 Ghose S. Optic nerve changes in hydrocephalus. *Trans Ophthalmol Soc UK* 1983; 103: 217-20.
- 29 Keltner JL. The disc that really isn't (hypoplastic disc syndrome). *Surv Ophthalmol* 1985; 29: 349-54.
- 30 Tamura EE, Hoyt CS. Oculomotor consequences of intraventricular haemorrhages in premature infants. *Arch Ophthalmol* 1987; 105: 533-5.
- 31 Benirschke K. Twin placentas in perinatal mortality. *NY State J Med* 1961; 61: 1499-508.
- 32 Melnick M. Brain damage in survivor after death of monozygotic co-twin. *Lancet* 1977; ii: 1287.
- 33 Roberts-Harry J, Green SH, Willshaw HE. Optic nerve hypoplasia: associations and management. *Arch Dis Child* 1990; 65: 103-6.

Vitreon, a new perfluorocarbon

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Abstract

We evaluated a new liquid perfluorocarbon, perfluorophenanthrene (Vitreon). This material has proved to be non-toxic in vitrectomised rabbit eyes for up to six weeks. Present investigation under FDA guidelines establishes both the safety and efficacy of Vitreon in human eyes. We used Vitreon for intraoperative hydrokinetic retinal manipulation in 15 patients. In cases of proliferative vitreoretinopathy (6), rhegmatogenous retinal detachment (5), giant retinal tear (2), retinal dialysis (1), and tractional retinal detachment (1) the retina was successfully reattached. Postoperatively two patients developed proliferative vitreoretinopathy necessitating further surgery, and one patient developed hypotony. Follow-up showed 100% reattachment rate with a mean duration of 6.3 months. Postoperative visual acuity ranges from light perception to 20/30.

Although a denser-than-water vitreous substitute (fluorosilicone oil) was studied in 1962 in retinal detachment surgery, its importance in complex cases such as giant tears was recognised much later.¹⁻³ The liquid fluorocarbons were initially introduced as oxygen carriers in medicine in 1966.⁴ Haidt *et al* used these substances for the first time as a vitreous substitute in 1982.⁵ Other investigators soon evaluated similar substances.⁶⁻⁹ Inherent in all perfluorocarbon liquids have been potential toxic effects on the retina within a short period of exposure.

In 1989 Nabih *et al* presented experimental evaluation of a new liquid fluorocarbon. The substance, perfluorophenanthrene (Vitreon), was found to be safe for up to six weeks in the vitrectomised eyes of New Zealand white rabbits if contact with the cornea was avoided.¹⁰ We used Vitreon as an intraoperative tool in the management of patients with complex retinal detachments in a limited phase I Food and Drug Administration (FDA) evaluation.

Patients and methods

Fifteen patients were recruited for this study, a phase I investigation under FDA guidelines. Informed consent was obtained under an

investigational protocol approved by the institutional review board at the Louisiana State University in New Orleans. Of the 15 patients six presented with proliferative vitreoretinopathy (PVR) stages C₂-D₂, five with rhegmatogenous retinal detachment and peripheral tear; two with giant retinal tear; one with retinal dialysis; and one with tractional retinal detachment (Table 1). Nine patients (60%) were male and six (40%) female. The mean age was 48.5 years, range 28 to 79 years. Preoperative visual acuity ranged from 20/400 to light perception.

A standard 20-gauge three-port pars plana approach was used for vitrectomy. Once removal of the vitreous was completed, the decision to use Vitreon intraoperatively was made. The Vitreon was initially injected through a blunt 20 to 27 gauge needle over the optic disc. In the learning phase of the study it was discovered that a partial air-fluid exchange was necessary during the Vitreon injection process in order to tamponade the peripheral retina (Fig 1A, B, C). After a partial air-fluid exchange was performed, injection of Vitreon over the posterior pole was completed at a slow rate to allow displacement of the subretinal fluid anteriorly. In rhegmatogenous retinal detachments with peripheral breaks the subretinal fluid was forced from a posterior to an anterior direction out of the peripheral tear. The same procedure was used for giant retinal tears as well as with retinal dialyses with unfolding of the retinal flap.

In complicated PVR cases, after membrane peeling a small amount of Vitreon was injected to determine if the retina would flatten at this point. If traction was still evident, more dissection from a posterior-to-anterior direction was attempted. The other option consisted in performing varying degrees of retinotomies or retinectomies. At this point partial air-fluid exchange was performed to tamponade the peripheral intact retina or the remaining retinal skirt in the case of a 360° retinectomy. The posterior vitreous cavity was then filled with Vitreon. Endolaser photocoagulation was then performed under Vitreon at the end of the operation when the retina was completely flat. An air-Vitreon exchange was then performed in all cases, with subsequent partial air-fluid exchange in an attempt to remove all the remaining Vitreon (Fig 1D, E). At this point a decision was made either to maintain the air inside the eye with subsequent SF₆ (15-20%) or C₃F₈ (10-15%) injection or to inject silicone oil for a longer tamponading effect. In eight eyes (53%) intraocular gas was used; in six eyes (40%) silicone oil (12 500 centistokes was used; and in one eye (7%) fluorosilicone oil (300 cSt) was used. A no 20 silicone band was then placed at the equator, and cryopexy was done at the sclerotomy sites.

Follow-up of the patients consisted in examin-

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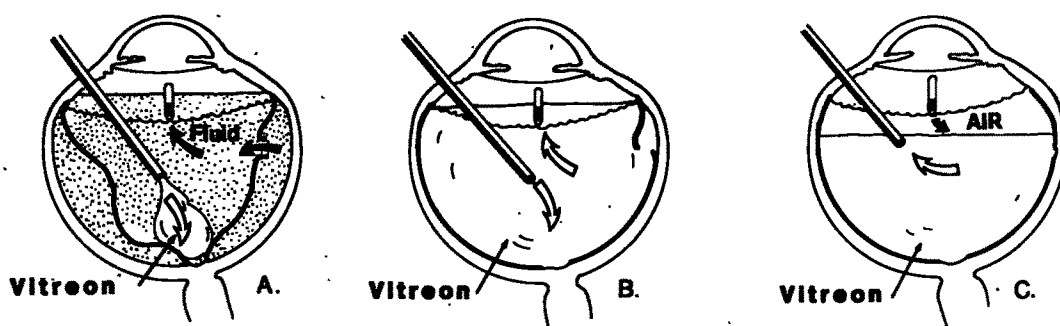
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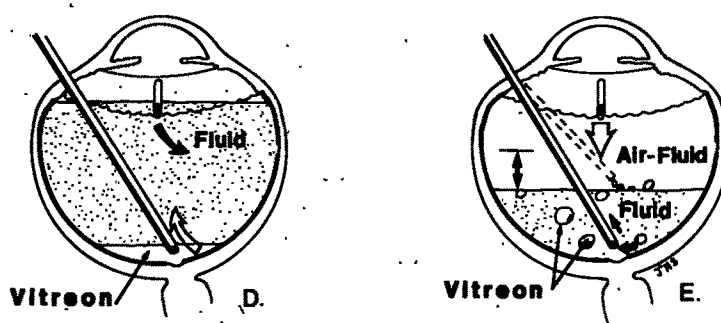
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Table 1 Preoperative profile

Proliferative vitreoretinopathy...	C ₂	2	6
	C ₃	1	
	D ₁	2	
	D ₂	1	
Rhegmatogenous retinal detachment			5
Giant retinal tear			2
Retinal dialysis			1
Tractional retinal detachment			1
Total			15



IMPLANTATION



REMOVAL

Figure 1 Vitreon implantation (A and B) with partial air-fluid exchange during injection process (C). Vitreon removal (D and E) with multiple fluid washings.

ations daily until stable, then weekly, bimonthly, and monthly for the first six months. Attention was directed to any excessive postoperative inflammation, cataract formation, intraocular pressure rise, membrane development, and retinal detachment. Any residual Vitreon noted in the eye postoperatively was removed by air-fluid or fluid-fluid exchange at the slit-lamp. Those eyes with silicone oil complications such as keratopathy, cataract formation, or emulsification were treated by immediate oil removal. Recurrent retinal detachments were repaired with another operation.

Results

Vitreon was effective in flattening the retinas in all 15 cases intraoperatively. In four cases intraoperatively, after removal of the Vitreon a redetachment occurred progressing from the periphery to the posterior pole. By careful examination we found that part of the subretinal fluid was trapped in the peripheral portion of the retina beyond the retinal tear. This situation necessitated a partial air-fluid exchange to the level of the retinal tear followed by further intravitreal injection of Vitreon. The peripheral air bubble flattened the anterior retina while the Vitreon reattached the posterior retina. No other intraoperative complications related to the use of Vitreon were experienced.

Table 2 shows the postoperative results of the 15 patients. No patients had any unusual inflammatory or toxic reaction related to the use

of Vitreon. One patient experienced a postoperative rise in intraocular pressure most likely related to the use of intraocular gas. Five patients had residual intraocular Vitreon bubbles, which were subsequently removed at the slit-lamp. Future cases then required multiple air-fluid exchange to ensure complete removal of the Vitreon. None of the patients with residual Vitreon showed an increased inflammatory reaction or keratopathy related to the Vitreon. One patient had a vitreous haemorrhage postoperatively secondary to an underlying bleeding diathesis. The blood cleared spontaneously over a six to eight week period.

Two patients experienced recurrent retinal detachments secondary to PVR. Both patients underwent successful surgery with membrane peeling and reattachment of the retina. Two patients in the series developed hypotony postoperatively with intraocular pressure of less than 5 mmHg, and another developed significant macular pucker. Overall, the retina was finally reattached in all the patients, with a mean follow-up duration of 6.3 months and a range of four to nine months. Postoperative visual acuities were better than or equal to the preoperative visual acuities in all cases except for patient five, who developed PVR necessitating another operation (Table 2).

Discussion

Perfluorophenanthrene (Vitreon) contains inherent physical properties necessary for a

Table 2 Postoperative results

Case	Age/Sex (Years)	Nature of Rd	Preop. vis. acuity	Intraop. complications	Postop. complications	Follow-up (months)	Postop. vis. acuity
1	50 M	Rhegmatogenous	CF	0	Residual Vitreous	5	20/60
2	32 M	RD with dialysis	CF	0	Exotropia	9	20/30
3	68 F	Rhegmatogenous	20/400	Reinjection due to redetachment	Vitreous haemorrhage; residual Vitreous; Increased IOP	8	20/200
4	39 F	Tractional with vitreous haeme	HM	0	0	8	20/200
5	48 M	Rhegmatogenous with choroidal detachment	HM	Choroidal detachment; reinjection due to redetachment	PVR with redetachment, reoperation	8	LP
6	64 M	Rhegmatogenous	LP	0	PVR with redetachment, reoperation with Vitreous	7	HM
7	58 F	PVR D ₂ and Macular hole	CF	0	Hypotony	7	CF
8	79 F	PVR D ₁	CF	0	0	4	CF
9	33 M	Rhegmatogenous with choroidal detachment	LP	Reinjection of fluoroallicone due to redetachment	PVR	5	20/70
10	28 M	Giant tear	HM	0	0	5	20/200
11	57 M	Giant tear	CF	0	Cataract	7	20/400
12	52 M	PVR C ₂	LP	0	Residual Vitreous	6	CF
13	49 M	PVR D ₁	LP	0	Residual Vitreous	5	CF
14	35 F	PVR C ₂	CF	0	Residual Vitreous	5	20/100
15	35 F	PVR C ₃	LP	0	Macular pucker	5	CF

CF=Counting fingers. HM=Hand motion. IOP=Intraocular pressure. PVR=Proliferative vitreoretinopathy. LP=Light perception. RD=Retinal detachment. M=Male. F=Female.

desirable denser-than-water temporary vitreous substitute. It has a specific gravity of 2.03, a viscosity of 8.03 cSt, and a boiling point of 215°C. It is immiscible with water, optically clear, and easily injected and removed through a small (20–27 gauge) needle. Past experimental studies with this substance have demonstrated no toxicity to culture-grown retinoblastoma cells.¹⁰ Vitreous was not toxic to the vitrectomised rabbit eyes when left in place for six weeks. No acute toxic or inflammatory reactions were noted during the operation or in the immediate postoperative period. In rabbit eyes fragmentation of the Vitreous into small globules in the vitreous cavity was noted at six weeks, which is later in onset than for previously studied liquid fluorocarbons.⁹ Postoperative electroretinographic recordings revealed no pathological changes in eyes tested. Light and electron microscopy of rabbit eyes at the end of follow-up showed retention of normal retinal architecture with no evidence of retinal toxicity. Corneal toxicity was noted, however, on injection of Vitreous into the anterior chamber of rabbit eyes as evidenced by corneal oedema.

In the present study we used Vitreous to facilitate reattachment of the retina in a variety of complex vitreoretinal disorders. None of the eyes showed any adverse or toxic effects directly related to its use, either intraoperatively or postoperatively. Even the eyes with inadvertent small amounts of Vitreous in the anterior chamber postoperatively failed to show any corneal toxic effects.

Modifications in the injection and removal techniques were made as experience was gained during the progression of the study. A few of the earlier patients were noted postoperatively to have small amounts of Vitreous remaining intraocularly. As a result all subsequent cases underwent multiple air-fluid exchanges in order to achieve complete removal of the Vitreous. Also during the injection a unique problem was confronted early in the series. In patients with rhegmatogenous retinal detachments with peripheral tears or holes Vitreous was used to

'steamroll' the subretinal fluid from the posterior pole out through the anterior retinal tear. This was achieved simply by injecting the Vitreous over the optic disc and observing the flattening effect as the Vitreous level rose. However, on removal of the Vitreous redetachment occurred in some cases as the liquid fluorocarbon level decreased. In these cases subretinal fluid was pushed by Vitreous pressure in the periphery past the retinal tear, not escaping through the defect. On removal of the Vitreous the subretinal fluid simply shifted back to its posterior gravity-dependent position. To avoid this complication in subsequent cases we performed a limited air-fluid exchange prior to filling the vitreous cavity with the Vitreous, causing the air bubble to tamponade the retina anterior to the tear. Vitreous injection over the optic disc was continued, slowly displacing the subretinal fluid out through the peripheral break, but not allowing it to go anterior to this point. Once the retina was flat, endolaser and/or cryotherapy was applied, and the air-fluid exchange was completed with resultant complete reattachment of the retina.

The diversity of preoperative diagnoses in our series demonstrates the potential utility of Vitreous in vitreoretinal surgery. Five patients presented with rhegmatogenous retinal detachments with peripheral breaks. Vitreous was used as described above, thus avoiding a posterior retinotomy for internal drainage of subretinal fluid. This step bypassed the potential complications associated with posterior retinotomies, such as bleeding and repopulation from the site of the retinotomy.¹¹

Many different techniques have been proposed for management of giant retinal tears; liquid fluorocarbons are the most recent method to be investigated.^{12–14} Two patients in our study presented with giant retinal tears. Vitreous injection after vitrectomy greatly simplified the repair of these difficult cases. Injection was begun over the optic disc. Further injection resulted in the unfolding of the retina, hydrokinetically tamponading the retina back against the retinal pigment epithelium with the patient in a supine

position. Posterior slippage of the retina was never encountered. Endolaser photocoagulation and/or retinal cryopexy was then performed as needed. Repair of retinal dialysis with detachment was accomplished in a similar fashion.

The diagnosis of proliferative vitreoretinopathy was encountered in six patients in our series, ranging from grade C₂ to D₂. Previous authors have reported the utility of liquid fluorocarbons in the management of PVR.¹⁵ Vitrectomy with intricate membranectomy was performed first. If the traction release from membranectomy was adequate, Vitreon was then injected with resultant good flattening of the retina. If some traction was still evident under Vitreon, further membranectomy was performed. Anterior loop traction was also considered in a few cases, with countertraction provided by the heavy vitreous substitute. In those patients with persistent traction, or initially severe PVR not amenable to membranectomy alone, relaxing retinotomies of varying degrees ranging from 180 to 360° were performed. Vitreon was then injected over the retina for stabilisation of the retina and further membranectomy, if indicated.

The Vitreon was removed from all eyes intraoperatively through fluid-Vitreon or air-Vitreon exchange. Postoperative vitreous replacement was accomplished with gas in eight cases, silicone oil in six cases, and fluorosilicone oil in one case.

Study of heavier-than water vitreous replacement substances was first begun in 1962 by Cibis, with injection of fluorosilicone oil into rabbit eyes.¹² Yet minimal interest was shown in this substance from the early 1960s until the late 1980s.¹⁶⁻¹⁸ Other investigators have demonstrated the utility of fluorosilicone oil as a denser-than-water vitreous substitute.^{3,19-22} There are, however, major disadvantages in the use of this heavy oil versus Vitreon intraoperatively. The first is the lighter specific gravity of fluorosilicone oil, 1.31 g as compared to 2.03 g for Vitreon. This difference allows for a more efficient tamponading effect with Vitreon than with fluorosilicone. The other disadvantage is found when comparing the viscosity of the two substances. The viscosity of fluorosilicone oil ranges from 300 to 10 000 cSt, thus greatly hampering both the injection and removal of this substance. Vitreon, with a viscosity of 8.03 cSt, is injected and removed from the eye as easily as balanced salt solution. This factor is important during intraoperative removal of the vitreous substitutes. Vitreon removal is accomplished easily by passive flow through a flute needle. The fluorosilicone oil, however, must be removed with an extrusion needle at high suction, which can be dangerous under air because of rapid swings of intraocular pressure when air is aspirated.

Previous studies of liquid fluorocarbons have been performed by various investigators. Miyamoto *et al* looked at two separate perfluoroether liquids, Freon E15 and Fomblin-H Fluorinated Fluid, finding both substances to be unsuitable vitreous substitutes owing to poor ocular tolerance of them.^{6,8} More recently Chang and associates⁹ studied perfluorotributylamine (C₁₂F₂₇N) in rabbit eyes and observed good intraoperative tolerance, but poor postoperative tolerance when left in the eye. They concluded

the substance was a poor long-term vitreous substitute because of the dispersion, foam cell response, and photoreceptor toxicity if the retina was exposed to it for longer than two weeks. Chang²³ subsequently reported on the use of perfluorotributylamine and perfluorodecalin intraoperatively in four patients with good intraocular tolerance. In the management of traumatic retinal detachments Chang reported the intraoperative use of three liquid perfluorocarbons (perfluorotributylamine, perfluorodecalin, and perfluorooctane) in 14 patients. Of 11 eyes, with at least six months' follow-up, eight (73%) had the retina anatomically reattached.²⁴ Giant retinal tears have also been successfully treated by intraoperative liquid fluorocarbons.¹⁴

In all previous studies of liquid fluorocarbons the intraocular tolerance of them has been shown to be very poor when left in the eye postoperatively.^{6,9} The properties of the ideal denser-than-water vitreous substitute must also include an inert nature providing ample ocular tolerance. Investigation of Vitreon has proceeded in a step-wise fashion. The first investigation established good ocular tolerance in rabbit eyes for up to six weeks.¹⁰ The next phase of study is presented here, with the establishment of good ocular tolerance in human eyes intraoperatively. The next step in the order of progression will be to leave the Vitreon in human eyes postoperatively until the formation of a firm chorioretinal scar. Thus Vitreon would provide a short-term tamponading effect that is occasionally desirable in complicated cases. We are now evaluating this phase of the study.

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The Vitreon was donated by Vitrophage Inc, Downer's Grove, IL, USA.

- 1 Cibis PA, Becker B, Okun E, Cansan S. The use of liquid silicone in retinal detachment surgery. *Arch Ophthalmol* 1962; 68: 590-9.
- 2 Cibis PA. Vitreous transfer and silicone injections. *Ophthalmology* 1964; 68: 983-97.
- 3 Peyman GA, Smith RT. Use of fluorosilicone to unfold a giant retinal tear. *Int Ophthalmol* 1987; 10: 149-51.
- 4 Clark LC Jr, Gollan F. Survival of mammals breathing organic fluids equilibrated with oxygen at atmospheric pressure. *Science* 1966; 152: 1755-6.
- 5 Haidt SJ, Clark LC, Ginsberg J. Liquid perfluorocarbon replacement of the eye. *Invest Ophthalmol Vis Sci* 1982; 22 (suppl): 233.
- 6 Miyamoto K, Refojo MF, Tolentino FI, Fournier GA, Albert DM. Perfluoroether liquid as a long-term vitreous substitute: an experimental study. *Retina* 1984; 4: 264-8.
- 7 Zimmerman NJ, Faris D. The use of N-perfluorocarbon amines in complicated retinal detachments. *Invest Ophthalmol Vis Sci* 1984; 25 (suppl): 258.
- 8 Miyamoto K, Refojo MF, Tolentino FI, Fournier GA, Albert DM. Fluorinated oils as experimental vitreous substitutes. *Arch Ophthalmol* 1986; 104: 1053-6.
- 9 Chang S, Zimmermann NJ, Iwamoto T, Ortiz R, Faris D. Experimental vitreous replacement with perfluorotributylamine. *Am J Ophthalmol* 1987; 103: 29-37.
- 10 Nabih M, Peyman GA, Clark LC, *et al*. Experimental evaluation of perfluorophenanthrene as a high specific gravity vitreous substitute: a preliminary report. *Ophthalmic Surg* 1989; 20: 286-93.
- 11 Machemer R, McCuen BW II, de Juan E Jr. Relaxing retinotomies and retinectomies. *Am J Ophthalmol* 1986; 102: 7-12.
- 12 Machemer R, Allen AW. Retinal tears 180° and greater: management with vitrectomy and intravitreal gas. *Arch Ophthalmol* 1976; 94: 1340-6.
- 13 Peyman GA, Schulman JA. *Intravitreal surgery: principles and practices*. Norwalk, Connecticut: Appelton-Century-Crofts, 1986: 294-303.

- 14 Chang S, Lincoff H, Zimmerman NJ, Fuchs W. Giant retinal tears: surgical techniques and results using perfluorocarbon liquids. *Arch Ophthalmol* 1989; 107: 761-6.
- 15 Chang S, Ozmert E, Zimmerman NJ. Intraoperative perfluorocarbon liquids in the management of proliferative vitreoretinopathy. *Am J Ophthalmol* 1988; 106: 668-74.
- 16 Watzke RC. Silicone retinopexies for retinal detachment: a long-term clinical evaluation. *Arch Ophthalmol* 1967; 77: 185-196.
- 17 Moreau PG. Les silicones intra-oculaires dans les décollements de rétine désespérés. *Ann Oculist (Paris)* 1967; 200: 257-65.
- 18 Labelle P, Okun E. Ocular tolerance to liquid silicone: an experimental study. *Can J Ophthalmol* 1972; 7: 199-204.
- 19 Paylor R, Peyman GA, Badri S. Effects of intravitreal injection of fluorosilicone oil after vitrectomy in the rabbit eye. *Can J Ophthalmol* 1987; 22: 251-3.
- 20 Peyman GA, Smith RT, Charles H. Injection of fluorosilicone oil and pars plana vitrectomy for complex retinal detachment. *Can J Ophthalmol* 1987; 22: 276-8.
- 21 Liu KR, Peyman GA, Miceli MV. Experimental evaluation of low-viscosity fluorosilicone oil as temporary vitreous substitute. *Ophthalmic Surg* 1989; 20: 720-5.
- 22 Gremillion CM, Peyman GA, Liu KR, Naguib KS. Fluorosilicone oil in the treatment of retinal detachment. *Br J Ophthalmol* 1990; 74: 643-6.
- 23 Chang S. Low viscosity liquid fluorochemicals in vitreous surgery. *Am J Ophthalmol* 1987; 103: 38-43.
- 24 Chang S, Reppucci V, Zimmerman NJ, Heinemann MH, Coleman DJ. Perfluorocarbon liquids in the management of traumatic retinal detachments. *Ophthalmology* 1989; 96: 785-92.

MINI REVIEW

Management of dysthyroid eye disease

Surgical decompression

The pathogenesis of dysthyroid eye disease continues to be an enigma though immune mechanisms with infiltration of the extraocular muscles by T cells are certainly involved. The patient may suffer visual loss from optic nerve compression at the orbital apex or, in cases of gross proptosis with chemosis and failure of the lids to close, corneal drying, ulceration, and endophthalmitis. Both of these conditions require urgent intervention.

If there is endophthalmitis with severe proptosis and chemosis, then surgical orbital decompression should be carried out as soon as possible. The only reason for any brief delay would be to bring concomitant hyperthyroidism under control to avoid the risk of thyroid crisis reaction. Decompression¹ may be via a Caldwell-Luc approach, allowing decompression into the ethmoid space and the antrum on both the medial and if necessary lateral sides of the infraorbital nerve. Other surgeons prefer the translid approach, in which the incision through the nasal and medial parts of the lower lid gives good access to the same ethmoidal and antral spaces from the orbital side. Where maximal decompression is required, some surgeons add a third wall, namely the lateral wall, to the decompression, but it is rarely necessary to include the orbital roof as well, with a significant rise in morbidity. Once the necessary space has been opened by removal of bone, the periosteum should be incised from posterior to anterior with longitudinally running incisions to allow the tense orbital fat to herniate outwards.² To reduce the risk of producing an A-pattern of esotropia, which commonly follows successful orbital decompression, Koornneef² has recommended that in the anterior part of the orbit the periosteal incisions run circumferentially rather than postero-anteriorly to minimise the damage to the complex orbital connective tissue framework which is essential for normal ocular movements. Unless the ophthalmologist is fully familiar with orbital and sinus anatomy it is usually preferable to carry out such surgery together with his ear, nose, and throat colleague so that he does the bone work and the eye surgeon carries out the periorbital incisions and the last stage of the decompression.

When optic nerve function is threatened by the enlarged ocular muscles compressing the nerve at the orbital apex, it is essential that the decompression goes back as far as possible on the medial side of the orbit to relieve the pressure. Although this may be achieved by either of the two routes mentioned above, I prefer the direct anterior ethmoidectomy route via an incision along the lateral side of the nose, which gives best access to the posterior ethmoidal area practically down to the optic foramen.

Some surgeons carry out orbital decompression for purely cosmetic reasons, and the Tessier approach,³ turning down a large frontal skin flap from behind the hairline, gives good access to all four orbital walls, and the periorbital can then be incised in all four quadrants to give excellent decompression with minimal risk of altering the ocular movements. The operation takes a long time.

Medical decompression

Surgical decompression may be the first choice for some

ophthalmologists. Others prefer to consider medical decompression, using high-dose oral prednisolone, 80-100 mg daily, provided that there is no contraindication such as previous tuberculosis or peptic ulceration. The addition of cyclosporin to prednisolone is also effective; it permits a lower total dose of prednisolone and is more tolerable to the patient. Recently intensive intravenous methyl prednisolone (0.5 g in 200 ml of isotonic saline over 30 minutes, which can be repeated after 48 hours) has proved to be effective, but careful medical monitoring is required because of the cardiovascular risks.⁴ If patients having corticosteroid therapy are not showing signs of improvement in visual acuity after 48 hours, it may still be necessary to change to surgical decompression. Even when the patient does respond well to the steroid treatment, it is not always easy to reduce the dosage over the next few weeks to low levels without the risk of recurrence of symptoms of optic neuropathy. If the maintenance dose has to be 25 mg of prednisolone or higher each day, many patients will not accept the frequent side effects that may accompany such levels.

Radiotherapy

Recently a third method of decompression has come back into vogue, namely radiotherapy,^{5,6} because improvements in the technique of administration together with the use of megavoltages from a linear accelerator are giving good results. Analysis of the results of such therapy in 311 patients treated over 20 years at Stanford showed improvement in soft tissue involvement, in proptosis, and in optic neuropathy. Male patients still requiring treatment for hyperthyroidism responded less favourably. The patients were treated with 2000 cGy in 10 fractions in the majority of cases. Those treated with 3000 cGy in 15 fractions of 200 cGy did not suffer additional complications but neither did they have any improved outcome. Of these patients 29% had ocular surgery following the radiotherapy, and in most cases this was for diplopia with excellent results. Fears that the radiotherapy would increase orbital fibrosis and diplopia were not realised.

New tests

Pain, tenderness, and increased conjunctival injection are being used as indicators of active inflammation⁷ within the orbit, and the proposal is that at such time immunosuppression by either radiotherapy or corticosteroids would have the best opportunity of being effective. Methods of detecting early dysthyroid optic neuropathy have included the pattern electroretinogram (PERG) and cortical visual evoked potentials (CVEPs), but neither test is as useful as colour contrast sensitivity along the tritan (blue) axis.⁸ The tritan sensitivity losses increase in magnitude progressively in line with increasing severity of dysthyroid optic neuropathy as estimated by the usual clinical indicators. These tests may help in identifying the most useful time at which to attempt more active intervention.

Diplopia

One of the more debilitating symptoms in this condition is

double vision. Teaching in the past used to recommend that the ocular movements must have been shown to be stable for at least two years before ocular muscle surgery could be contemplated. This waiting time has now been reduced to six months of demonstrable stability by means of serial Hess charts and records of the field of binocular single vision. Rather surprisingly, botulinum neurotoxin A injections into the tight rectus muscles within one year of the onset of diplopia have sometimes given improved ocular rotations lasting much longer than the normal two months after such an injection.⁹ In seven out of 43 patients a long-lasting and stable result followed the use of one or two injections only. Since botulinum toxin cannot have a lytic effect on established fibrosis, it must be working in some other manner. In five patients with ophthalmic Graves' disease of recent onset length-tension measurements during surgery¹⁰ under topical anaesthesia suggested that the restricted ocular movements were caused by active muscle contraction in the early phase of the disease and not by fibrosis.

Prospects

Measuring blue contrast sensitivity, and recognising clinically the periods of active inflammation, will enable treatments with radiotherapy, corticosteroids, or botulinum toxin A to

be given at the optimal time. Eventually the immunopathogenic mechanisms will be identified and stopped before the disease process becomes established.

PETER FELLS

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- 1 Fells P. Orbital decompression for severe dysthyroid eye disease. *Br J Ophthalmol* 1987; 71: 107-11.
- 2 Koornneef L. Eyelid and orbital fascial attachments and their clinical significance. *Eye* 1988; 2: 130-4.
- 3 Mourits MP, Koornneef L, Wiersinga WM, Prummel MF, Berghout A, van der Gaag R. Orbital decompression for Graves' ophthalmopathy by inferomedial, by inferomedial plus lateral, and by coronal approach. *Ophthalmology* 1990; 97: 636-41.
- 4 Kendall-Taylor P, Crombie AL, Stephenson AM, Hardwick M, Hall K. Intravenous methylprednisolone in the treatment of Graves' ophthalmopathy. *Br Med J* 1988; 297: 1574-8.
- 5 Harnett AN, Doughty D, Hirst A, Plowman PN. Radiotherapy in benign orbital disease. II: Ophthalmic Graves' disease and orbital histiocytosis X. *Br J Ophthalmol* 1988; 72: 289-92.
- 6 Petersen IA, Kriss JP, McDougall IR, Donaldson SS. Prognostic factors in the radiotherapy of Graves' ophthalmopathy. *Int J Radiation Oncology Biol Phys* 1990; 19: 259-64.
- 7 Mourits MP, Koornneef L, Wiersinga WM, Prummel MF, Berghout A, van der Gaag R. Clinical criteria for the assessment of disease activity in Graves' ophthalmopathy: a novel approach. *Br J Ophthalmol* 1989; 73: 639-44.
- 8 Potts M, Falcao-Reis F, Fells P, Buceti S, Arden GB. Colour contrast sensitivity, pattern ERGs and cortical evoked potentials in dysthyroid optic neuropathy. *Invest Ophthalmol Vis Sci* 1990; 31: ARVO abstract 932.
- 9 Lyons CJ, Vickers SF, Lee JP. Botulinum toxin therapy in dysthyroid strabismus. *Eye* 1990; 4: 538-40.
- 10 Simonsz HJ, Kommerell G. In Graves' disease, increased muscle tension and reduced elasticity of affected muscles is primarily caused by active muscle contraction. *Neuro-ophthalmology* 1989; 9: 243-6.

CASE REPORTS

Epibulbar choristoma and microphthalmia: a report of two cases

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Abstract

The simultaneous ipsilateral presence of an epibulbar choristoma and microphthalmia has rarely been reported. We present two such cases, one of which is associated with bone formation, and we consider a possible pathogenetic mechanism.

The simultaneous occurrence of epibulbar choristomas and microphthalmia has been

reported¹⁻³ but is extremely rare. It is not known whether the association is causal or incidental, though intraocular involvement by epibulbar choristomas apparently without associated microphthalmia has been reported.^{4,5}

Case reports

CASE 1

An otherwise healthy 16-year-old male presented to the Kikuyu Eye Department in Kenya with a large growth protruding through the left interpalpebral fissure (Fig 1). The lesion had been present from birth. On examination the orbit was clinically anophthalmic. The mass was excised by subtotal exenteration for cosmetic reasons.

On gross examination the lesion consisted of two lobes of tissue connected by a short pedicle. The total anteroposterior length was 32 mm. The posterior lobe was 20 mm and the anterior lobe

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Figure 1 Case 1. Clinical photograph of orbital lesion protruding through the left interpalpebral fissure. Numerous hairs are present on the exposed portion of the mass.

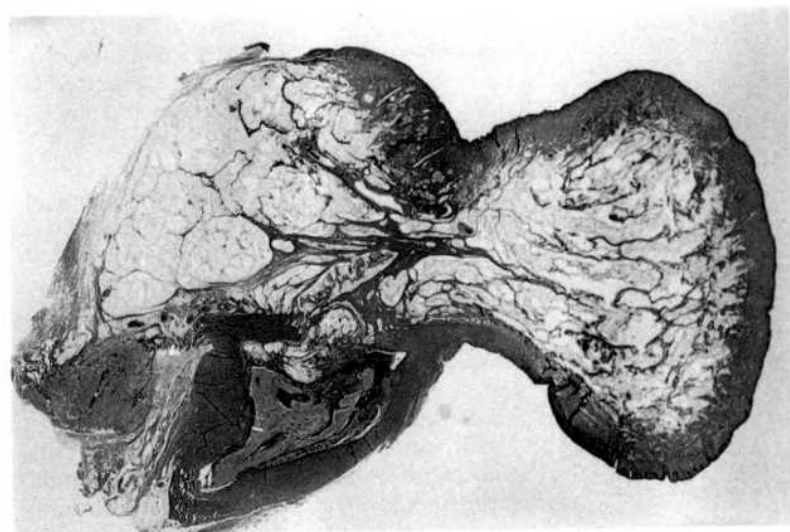


Figure 2 Case 1. A nodule of fibroadipose tissue covered by skin is attached by means of a short pedicle to orbital connective tissue, on the inferior aspect of which is a disorganised, microphthalmic globe. The superior part of the 'scleral' condensation surrounding the globe is deficient and corresponds to a colobomatous defect in the developing choroid and retinal pigment epithelium. (Verhoeff $\times 3.5$.)

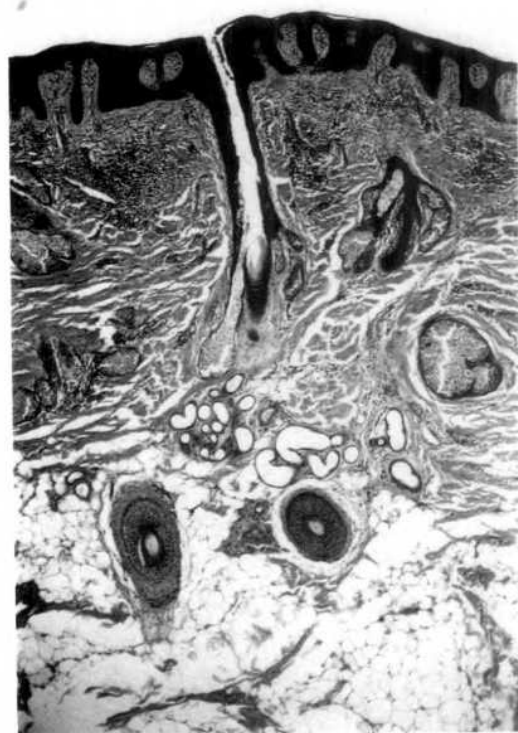


Figure 3 Case 1. Section of the 'dermolipoma' showing adipose tissue covered by skin replete with adnexal structures. There is a mild lymphocytic infiltration of the reticular dermis. (H and E, $\times 28$).

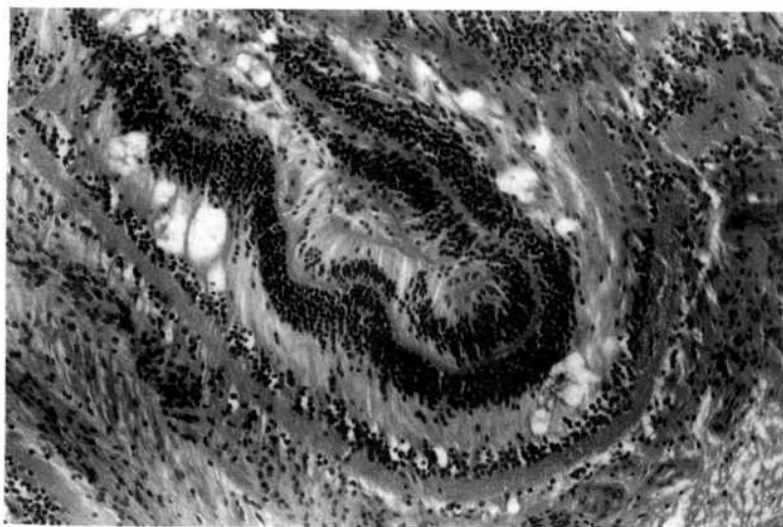


Figure 4 Case 1. The tissue occupying the cavity of the globe includes folds of differentiated neuroretina. (H and E, $\times 125$.)



Figure 5 Case 1. A limited anterior chamber is lined on its outer 'corneal' aspect by a Descemet's membrane which extends in part over the primitive uveal component of the anterior segment. (H and E, $\times 125$.)

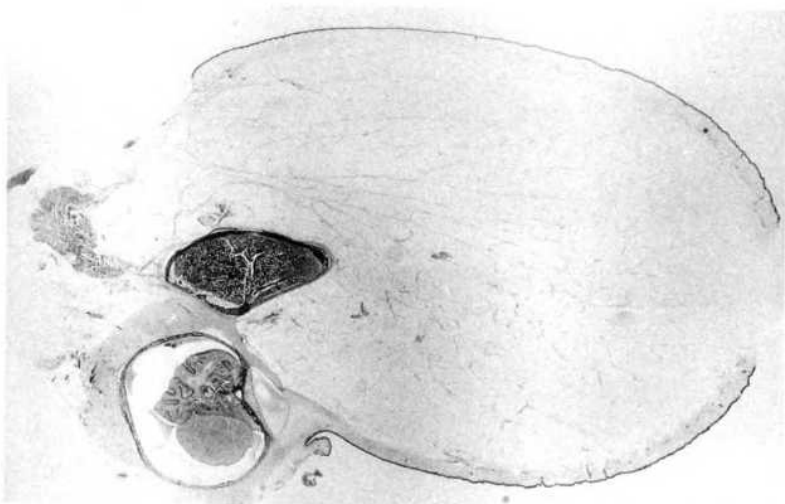


Figure 6 Case 2. A large rounded mass of adipose tissue is covered by skin with sparse adnexal elements and includes a nodule of bone at the base. A microphthalmic globe is also present, the posterior segment of which is occupied by folds of detached retina. (H and E, $\times 2.8$.)

15 mm in transverse diameter. Hair-bearing, pigmented, keratinised skin covered the anterior lobe and pedicle, while the posterior portion of the lesion appeared to be a mass of orbital fat

without epithelium. Sagittal sectioning revealed a 5 mm diameter pigmented remnant of presumed ocular tissue located within the inferior part of the posterior lobe.

Histologically the anterior aspect of the specimen consisted of a pigmented, keratinising squamous epithelium covering adipose tissue subdivided by connective tissue septae (Fig 2). The epithelium displayed maturation typical of epidermis (Fig 3). Numerous pilosebaceous apparatuses, sweat glands, and rete pegs were embedded in a dense layer of subepithelial fibrous connective tissue. Within the dermis of the inferior portion of the anterior lobe was a mild chronic inflammatory infiltrate, possibly caused by prolonged rubbing of this part of the mass on the adjacent malar eminence. The adipose tissue in the anterior lobe was in continuity with similar tissue in the posterior lobe through the central pedicle. In the inferior portion of the posterior lobe lay a microphthalmic globe, the central cavity of which was filled by folds of partially gliosed neural tissue displaying frequent evidence of retinal differentiation (Fig 4). This was surrounded by a densely pigmented and richly vascularised tissue consistent with a disorganised choroid and retinal pigment epithelium, which was in turn surrounded by a coarsely organised layer of collagen. In the anterior portion of the fibrous tissue layer a Descemet's membrane was present, separated from an incompletely formed anterior chamber by a single layer of attenuated cells (Fig 5). Some sections revealed an extensive defect in the superior aspect of the 'scleral' condensation, this defect being filled with adipose tissue continuous with that present in the orbit. A large-calibre blood vessel traversed the tissue within this coloboma. Lens material was not evident in sections taken from multiple levels. Foci of dystrophic calcification and lamellar bone formation were present in the degenerate retina and primitive uvea. A well defined but gliosed optic nerve could be seen leaving the posterior part of the globe.

CASE 2

A 1-year-old female from Ghana presented with a large mass protruding from an interpalpebral fissure. This mass was excised by subtotal exenteration.

On gross examination the specimen consisted of an elongated sphere measuring 38 mm in anteroposterior length by 25 mm transversely. The anterior two-thirds of the mass was covered by pigmented, hair-bearing skin. The posterior one-third of the lesion was composed of adipose tissue. An 8 mm diameter apparent globe remnant was present in the posterior part of the specimen inferiorly. Adjacent to the globe was an 8 $\times$ 5 mm ellipse of calcified material.

Microscopic examination showed that the lesion was covered anteriorly by mature, stratified, squamous, keratinising epithelium with a deeply pigmented basal layer. Near a reflection of tissue posteriorly the epithelium became non-keratinising, but no goblet cells were present in this part of the epithelium. Deep to the epithelium was a well-defined dermal layer

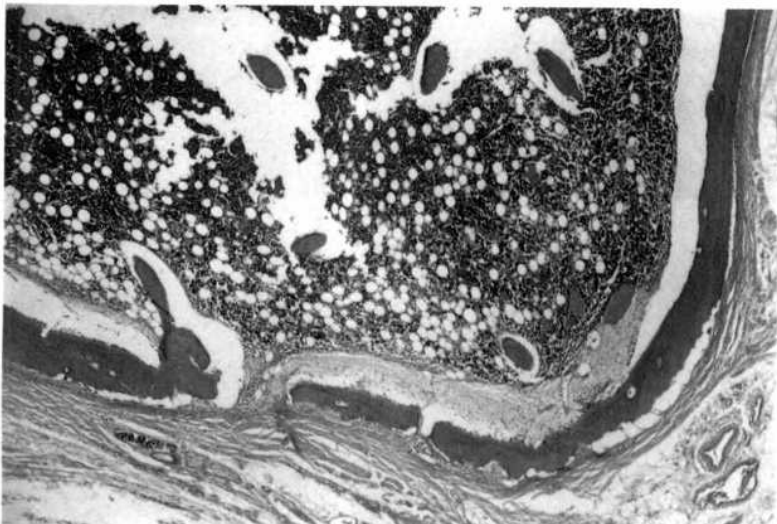


Figure 7 Case 2. Part of the choristomatous osseous tissue in the form of a shell surrounding haemopoietic marrow with sparse interlacing trabeculae. (H and E, $\times 30$.)

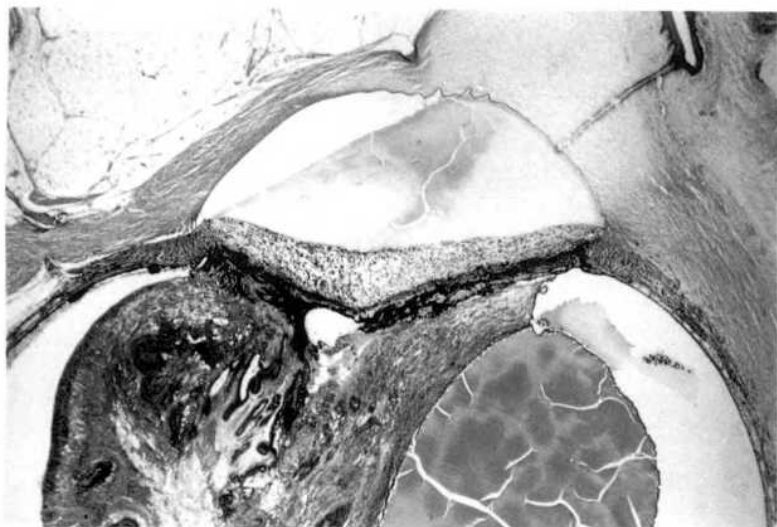


Figure 8 Case 2. A reasonably well formed anterior chamber is backed by iridociliary pigment epithelium which merges with a mass of detached and folded retinoglial tissue. Subretinal exudate is also seen. (H and E, $\times 15$.)

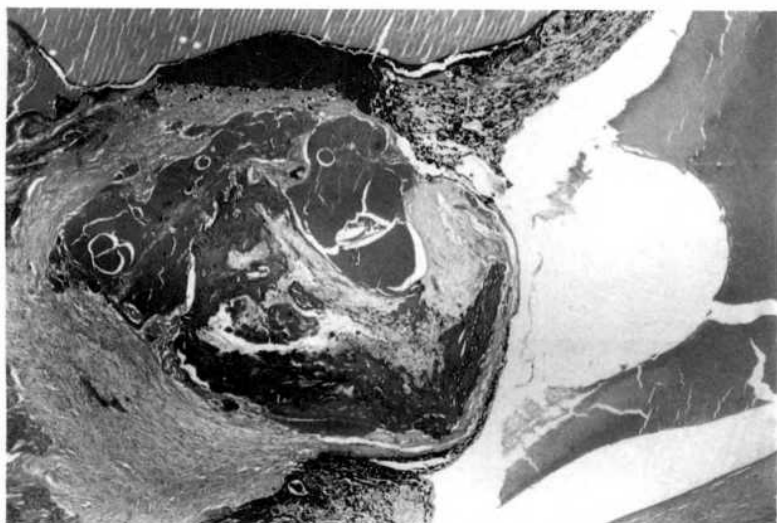


Figure 9 Case 2. A section cut at a different level from the previous samples shows a remnant of cataractous and partially organised lens tissue. It is separated from the anterior chamber by a narrow rim of pigmented uveal tissue. (H and E, $\times 30$.)

composed of dense connective tissue, containing fine hair follicles and numerous sweat glands. The bulk of the mass consisted of mature adipose

tissue continuous posteriorly with the intraorbital fat (Fig 6). Connective tissue septa coursed through the intraorbital and intralesional adipose tissue. The calcified lesion in the posterior aspect of the specimen was found to be lamellar bone with a central cavity containing adipose tissue and bone marrow (Fig 7). Fibrous connective tissue covered the bone on three sides and the remaining surface was in direct contact with the sclera of the globe remnant at the insertion site of an extraocular muscle.

The globe remnant had a fibrous tissue coat, the anterior fibres being more regularly orientated than those situated posteriorly. A Descemet's membrane and single layer of cuboidal cells lined the posterior aspect of this immature cornea, posterior to which was an anterior chamber filled with exudate (Fig 8). The angle and iris were immature, though some evidence of trabecular tissue was present in the angle, and dilator pupillae fibres were seen in the iris. The lens was cataractous (Fig 9). The central cavity of the globe was filled with disorganised neuroglial tissue attempting to form layers. Subretinal exudate separated this from a heavily pigmented retinal pigment epithelial layer covering a well developed choroid. Foci of intraocular calcification and early dystrophic lamellar bone formation were present anterior to the lens and within the disorganised retinal tissue. At least one extraocular muscle was inserted into the globe. An apparently normal optic nerve could be seen leaving the globe posteriorly.

Discussion

Each of the cases we have presented had epibulbar masses comparable with lesions that others have called dermolipomas. However, adnexal structures, especially pilosebaceous apparatuses, have been said to be unusual in dermolipomas,^{6,7} and it may be that the lesions in question are simply epibulbar extensions of orbital fat covered by skin. Sinha and Mishra⁸ have reviewed the postulated aetiologies of dermoid choristomas. These hypotheses direct attention towards a superficial cause and do not adequately explain the extensive orbital involvement of many 'dermolipomas', including the cases we present. Conversely, the presence of mature cancellous bone in the second case, similar to a case presented by Ferry and Hein,⁹ probably argues for the genuinely choristomatous character of the masses.

The degree of development reached by the ocular tissue in the two cases differed. In the first case the presence of a Descemet's membrane, retinal differentiation sufficient to include ganglion cells, and the degree of development of the choroid and optic nerve suggest maturation to at least the 110 mm (16 weeks) stage. The failure to detect any lens tissue implies a resorptive process as it is unlikely that development of the globe could have proceeded to the level observed in its absence. The incomplete formation of the cornea and anterior chamber may also have been a consequence of an abbreviated lens presence. It is possible that maturation of the globe as a whole was arrested shortly

before the end of the fifth month, as by that time the sclera should have been approaching a definitive stage, and some attempt at a retinal circulation might have been expected. The second case showed more advanced development, probably well into the seventh month, as judged by the presence of a well defined dilator pupillae muscle and anterior chamber structures.

It is tempting to try to link the incomplete ocular development with the presence of epibulbar lesions in these cases. It could be reasoned in the first case that a putative excess of precursor adipose tissue early in embryogenesis had prevented adequate contact between the optic vesicle and the lens plate such that the lens failed to develop properly, leading to its subsequent resorption. Invagination of similar tissue into the primary optic fissure might account for the coloboma, while continued proliferation of adipose tissue could have produced the epibulbar mass.

In respect of the second case development was much more advanced, and it is difficult to ascribe the involutinal changes to interference by adipose tissue lying outside the globe, though excessive proliferation of the orbital adipose

tissue in the later stages of intrauterine life could account for the epibulbar lesion. Whether this admittedly speculative attempt to explain the coincidence of microphthalmia and epibulbar choristoma has any validity is unknown.

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- 1 Svoboda JR, Madge G, Geeraets WJ. Corneal lipodermoid with microphthalmos. *Am J Ophthalmol* 1968; 65: 36-42.
- 2 Andersen SR, Wangsa S, Limpaphayom P. Degenerative apparent anophthalmia with complex choristoma of orbit: a clinicopathological case report. *Ophthalmologica* 1979; 178: 321-6.
- 3 Duke-Elder S. The Cornea. *System of ophthalmology*. London: Kimpton, 1964; 3(2): 535-8.
- 4 Schulze RR. Limbal dermoid tumour with intraocular extension. *Arch Ophthalmol* 1966; 75: 803-5.
- 5 Garner LL. Dermoid of the limbus involving the iris angle and lens. *Arch Ophthalmol* 1951; 46: 69-72.
- 6 Spencer WH, Zimmerman LE. Conjunctiva. In: Spencer WH, ed. *Ophthalmic pathology: an atlas and textbook*. 3rd ed. Philadelphia: Saunders, 1985; 1: 121-8.
- 7 Nicholson DH, Green WR. Tumors of the eye, lids and orbit in children. In: Harley RD, ed. *Pediatric Ophthalmology*. 2nd ed. Philadelphia: Saunders, 1983; 2: 1238-42.
- 8 Sinha PN, Mishra MB. Corneal dermoid: report of a case. *Am J Ophthalmol* 1950; 33: 1137-41.
- 9 Ferry AP, Hein HF. Epibulbar osseous choristoma within an epibulbar dermoid. *Am J Ophthalmol* 1970; 70: 764-6.

Bilateral eyelid myxomas in Carney's complex

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Abstract

A 21-year-old man with a history of an excised soft tissue mass of the groin and spotty cutaneous pigmentation underwent excision of nodules of the right lower and left upper eyelids. The patient subsequently had a cutaneous mass of the left ear removed. All excised lesions were classified as myxomas. A diagnosis of multiple myxoma, spotty pigmentation, and endocrine overactivity (Carney's) complex was made.

In 1985 Carney and associates described a complex consisting of various combinations of myxomas, spotty cutaneous pigmentation, and endocrine overactivity.¹ The importance of recognition of this complex is that a significant proportion of patients with the complex have a cardiac myxoma, a potentially lethal lesion.^{1,2}

Case report

A 21-year-old man with lesions of the right lower and left upper eyelids which had been present for two years was examined (Figs 1A, B). There were 0.5 × 0.5 × 0.5 cm soft nodular lesions of the right lower and left upper eyelids. Small, inconspicuous areas of spotty pigmentation were present on the patient's face. The rest of the ophthalmic examination showed nothing abnormal.

The eyelid nodules were excised. Histological examination of the right lower eyelid lesion showed a fibromyxoid stroma covered by epidermis. The left upper eyelid lesion was composed of a loosely myxoid stroma containing spindle and stellate cells covered by epidermis (Figs 2A, B). The patient's past history was significant for a recently excised soft tissue lesion of the left groin. Review of the histology of the groin lesion showed findings similar to those of the eyelid lesions.

Approximately one month after examination a 0.8 × 0.6 × 0.3 cm cutaneous nodule of the left ear

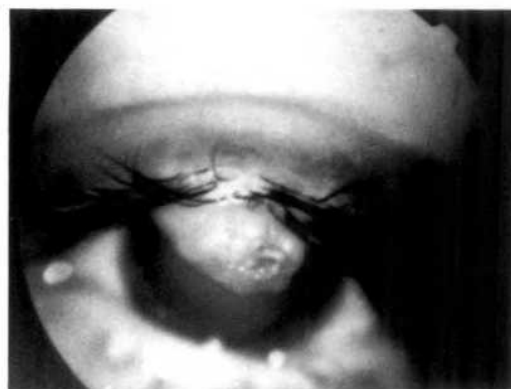


Figure 1B Left upper eyelid nodule is similar in appearance to the right lower eyelid nodule.

was excised. Histological examination showed findings virtually identical to those of the eyelid and groin lesions. The groin, eyelid, and ear lesions were classified as myxomas. Owing to the spotty pigmentation and the histopathological appearance of the excised lesions the diagnosis of Carney's complex was made. The results of the rest of the physical examination were normal. An echocardiogram and serum cortisol level were normal. Subsequently it was found that one of the patient's parents and two of his siblings had multiple myxomas and spotty cutaneous pigmentation.

Discussion

The presence of multiple myxomas, spotty pigmentation, and a positive family history suggest a diagnosis of Carney's complex. Carney and coworkers found reports of 36 patients in the literature with various combinations of myxomas, spotty cutaneous pigmentation, and endocrine overactivity, and they combined these patients with four new patients in their original definition of this complex.¹ There are various histological counterparts of the spotty cutaneous pigmentation including lentigo, ephelis, junctional naevus, compound naevus, and atypical

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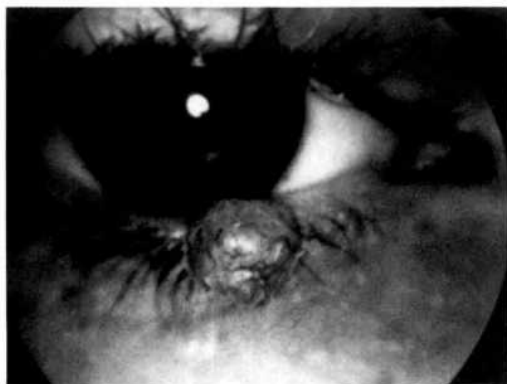


Figure 1A Nodular, white to yellow right lower eyelid lesion.

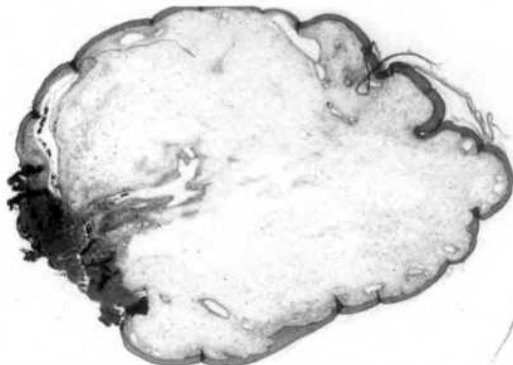


Figure 2A The left upper eyelid nodule is composed of a myxoid stroma covered by overlying epidermis. (Haematoxylin-eosin, ×153.)

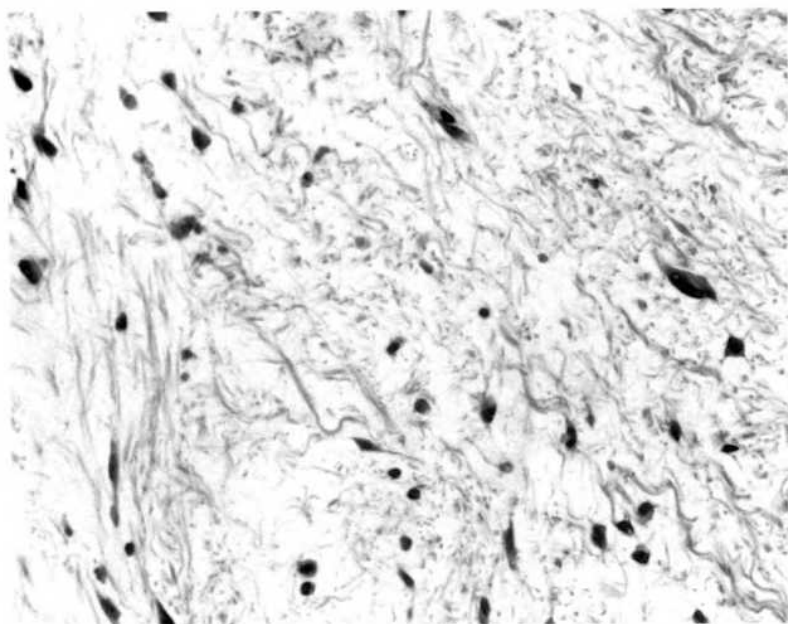


Figure 2B Higher magnification of the left upper eyelid lesion shows spindle and stellate shaped cells in a myxoid background. (Haematoxylin-eosin, $\times 300$.)

blue naevus.¹ Our patient had spotty facial pigmentation with the clinical appearance of benign naevi; none of his pigmented lesions were biopsied.

Endocrine abnormalities in patients with this complex include adrenocortical disease, Sertoli cell tumours, and acromegaly.¹ The presence of two of the three criteria is needed to make the diagnosis. A subsequent report suggests an autosomal dominant inheritance pattern to this complex.³ The syndrome may be due to a genetically determined malfunction of mesenchymal cells causing 'myxomatosis', akin to neurofibromatosis.² Several reports published after Carney and coworkers' original article

describe other patients with the complex.⁴⁻⁸

Ophthalmic findings in patients with this complex include spotty pigmentation of the eyelids, pigmented lesions of the caruncle or conjunctival semilunar folds, and myxomas of the eyelids.⁸ Cutaneous myxomas in this complex present most often in the skin of the head and neck, followed by the trunk, pelvic area, and limbs.² The cutaneous myxomas are most commonly of the eyelid, ear, and nipple. Eyelid myxomas are reported to occur in 10% of patients with the syndrome.⁸ It is important to note that cutaneous myxomas are detected prior to the cardiac myxoma in the majority of patients.² Therefore, in a patient with multiple cutaneous myxomas, spotty pigmentation, and/or endocrine overactivity, cardiac ultrasonography should be performed.

We thank Dr J Aidan Carney for examining the patient and providing information on his family.

The opinions or assertions contained herein are the private views of the authors and should not be construed as being official views of the Department of the Army or the Department of Defence

- 1 Carney JA, Gordon H, Carpenter PC, Shenoy V, Go VLW. The complex of myxomas, spotty pigmentation, and endocrine overactivity. *Medicine* 1985; **64**: 270-83.
- 2 Carney JA, Headington JT, Su WP. Cutaneous myxomas. A major component of the complex of myxomas, spotty pigmentation, and endocrine overactivity. *Arch Dermatol* 1986; **122**: 790-8.
- 3 Carney JA, Hruska LS, Beauchamp GD, Gordon H. Dominant inheritance of the complex of myxomas, spotty pigmentation, and endocrine overactivity. *Mayo Clin Proc* 1986; **61**: 165-72.
- 4 Reed OM, Mellette JR, Fitzpatrick JE. Cutaneous lentiginosis with atrial myxomas. *J Am Acad Dermatol* 1986; **15**: 398-402.
- 5 Leedman PJ, Cohen AK, Matz LR. The complex of myxomas, spotty pigmentation and endocrine overactivity. *Clin Endocrinol* 1986; **25**: 527-34.
- 6 Rowe MH, Mullany CJ, Leitt G. Spotty pigmentation and atrial myxoma: a case report of Carney's complex. *Med J Aust* 1988; **149**: 10-2.
- 7 Reinecke P, Frenzel H, Hort W, Willberg B. The combination of atrial myxoma and multiple skin myxomas: a characteristic symptom complex? *Dtsch Med Wochenschr* 1987; **112**: 1902-5.
- 8 Kennedy RH, Waller RR, Carney JA. Ocular pigmented spots and eyelid myxomas. *Am J Ophthalmol* 1987; **104**: 533-8.

LETTERS TO THE EDITOR

Adverse effects of subconjunctival injections of mydriatic agents

SIR,—The adverse effects of mydriatic agents are well documented. When using these drugs one must carefully consider the relevant medical history. The uveitic patient with early posterior synechiae and concomitant systemic disease is illustrative of this problem. We report a serious complication in a patient treated with mydriatic agents.

A 26-year-old male had a 10-day history of photophobia, fatigue, and fevers for several months. On examination his vision was 20/40 and the pupils were constricted secondarily to 270° posterior synechiae. He had hyperaemic conjunctivae, diffuse 'mutton-fat' keratic precipitates, and 3+ cells. Dilatation with topical and pledget soaked tropicamide 1% and phenylephrine 2.5% was unsuccessfully attempted. The patient returned 24 hours later, and a mixture of two drops (100 µl) each of tropicamide 1%, atropine 1%, and phenylephrine 10% was injected subconjunctivally at the inferior limbus of the right eye. This mixture comprised 7 mg of phenylephrine, 1 mg of atropine, and 1 mg of tropicamide. The patient immediately developed severe headache, dyspnoea, and diaphoresis. His pulse was 110 per minute and blood pressure of 160/110 mmHg.

He was taken to the emergency room, where he was found to be in respiratory failure. Chest x-ray revealed diffuse interstitial infiltrates not present on the previous day's films. The patient was intubated, and Swan-Ganz catheterisation revealed a pulmonary wedge pressure of 8 mm. He was transferred to the intensive care unit for management of non-cardiogenic pulmonary oedema. Subsequent diagnostic testing was consistent with a diagnosis of sarcoidosis. The pulmonary oedema resorbed and the patient was discharged on topical steroids with subsequent resolution of the iritis.

This is the first reported case of non-cardiogenic pulmonary oedema associated with the use of mydriatic drugs. Both atropine and tropicamide are anticholinergic drugs whose actions include relaxation of the circular muscle of the iris and paralysis of the ciliary muscle. The principal adverse cardiopulmonary effect of these drugs is tachycardia. Phenylephrine, a potent, direct-acting, and selective α_1 agonist exerts its main mechanism of action by stimulation of α receptors of the dilator pupillae.¹ Stimulation of these receptors can cause constriction of the systemic, pulmonary, and coronary arteries, leading to severe hypertension, headache, ventricular arrhythmias, myocardial infarction, and cardiac arrest.² It is conceivable that in our patient phenylephrine may have produced severe pulmonary vasoconstriction leading to alveolocapillary damage and consequent non-cardiogenic pulmonary oedema. In addition our patient had pre-existing pulmonary sarcoidosis, which may have increased his susceptibility to lung injury from other insults.

Subconjunctival injections of mydriatic agents to forcibly dilate pupils with synechiae is recommended³ and is commonly used in several eye centres. These injections, especially in hyperaemic conjunctivae, can lead to enhanced systemic absorption and serious complications. We advise extreme caution

when using this method of administering dilating agents.

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- 1 Lamberts DW, Potter ED. *Clinical ophthalmic pharmacology*. Boston: Little, Brown, 1987: 321.
- 2 Fraunfelder FT, Scafidi AF. Possible adverse effects from topical ocular 10% phenylephrine. *Am J Ophthalmol* 1978; 85: 447.
- 3 Duane TD. *Clinical ophthalmology*. Revised ed. Philadelphia: Lippincott, 1988: 4: chapter 43: 3.

Branch retinal artery occlusion in toxoplasma retinochoroiditis

SIR,—Although toxoplasma retinochoroiditis may cause retinal vein occlusion, vascular remodelling, and even retinochoroidal anastomosis,^{1,2} retinal artery obstruction is rare.^{3,5} We have recently studied a patient suffering from such a complication.

An 18-year-old student attended in March 1989, 24 hours after the sudden loss of inferotemporal field in the right eye, which was confirmed by automated perimetry. A branch artery occlusion was found in a corresponding area of focal retinochoroidal inflammation. Some areas of periphlebitis were also seen peripherally. Fluorescein angiography confirmed occlusion of the artery within the area of inflammation (Fig 1). Antibodies to toxoplasma were detected by latex agglutination at serum dilutions of more than 1:1000.

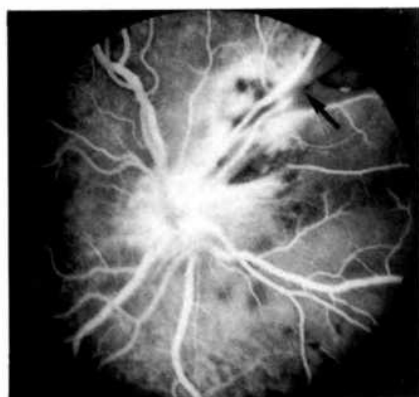


Figure 1 Fluorescein angiogram showing the active retinochoroidal inflammation and the occluded retinal arteriole (arrow).

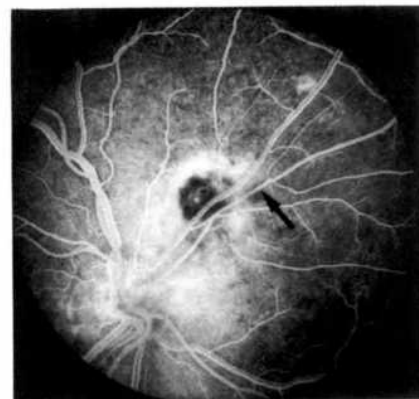


Figure 2 Fluorescein angiogram showing resolution of the inflammation and reperfusion of the retinal arteriole (arrow).

The patient was treated with clindamycin, 150 mg four times a day, and prednisolone 60 mg daily, reducing over eight weeks. At the end of this period the inflammatory focus had become inactive. Repeat fluorescein angiography demonstrated reperfusion of the artery (Fig 2). However, the field defect persisted.

This case confirms that field loss in toxoplasma retinochoroiditis can result from arterial occlusion. Arterial thrombosis is presumably caused by the intense adjacent inflammation. Corticosteroid and antimicrobial therapy⁶ may assist resolution of the inflammatory focus and should be considered when retinal vessels are involved and therefore at risk of occlusion. If, as in this case, occlusion has already occurred, retinal function may not recover despite resolution of the inflammation and reperfusion of the blood vessel.

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- 1 Gaynon MW, Boldey ED, Strahman ER, Fine SL. Retinal neovascularisation and ocular toxoplasmosis. *Am J Ophthalmol* 1984; 98: 585-9.
- 2 Gass JM. *Stereoscopic atlas of macular disease: diagnosis and treatment*. 3rd ed. St Louis: Mosby, 1987; 2: 464-9.
- 3 Owens PL, Goldberg MF, Busse BJ. Prospective observation of vascular anastomoses between the retina and the choroid in recurrent toxoplasmosis. *Am J Ophthalmol* 1979; 88: 402-5.
- 4 Braunstein RA, Gass JDM. Branch artery obstruction caused by acute toxoplasmosis. *Arch Ophthalmol* 1980; 98: 512-3.
- 5 Morgan CM, Gragoudas ES. Retinal artery occlusion associated with recurrent toxoplasmosis. *Arch Ophthalmol* 1987; 105: 130-1.
- 6 Lakhanpal V, Schocket SS, Nirankari VS. Clindamycin in the treatment of toxoplasmic retinochoroiditis. *Am J Ophthalmol* 1983; 95: 605-13.

Corneal penetration by tarantula hairs

SIR,—Tarantulas are large, hairy spiders belonging to the family Theraphosidae. Their popularity as pets parallels the increasing popularity of exotic pets in general. Although their bite is virtually harmless to humans, many species of New World tarantulas possess projectile urticating hairs on the dorsal surface of the abdomen.¹ When threatened, the spiders rapidly stroke their hind legs in a vibratory fashion on the dorsal hairs, catapulting a cloud of barbed hairs at the attacker. Some species may incorporate urticating hairs into their retreats or webs. These hairs, each possessing multiple barbs, are capable of penetrating deeply into skin, and causing intense and prolonged localised urticaria in humans.^{1,2} In addition to dermatological trauma tarantula hairs are capable of embedding into the ocular tissues and producing an inflammatory reaction in the eye.^{3,4} Due to its small calibre, offending hairs could easily be overlooked without a slit-lamp examination of the anterior eye segment.

A 13-year-old boy reported feeling severe foreign body sensation in both eyes within five minutes of stroking his pet tarantula. This was followed by intense pruritus, tearing, conjunctival injection, and eyelid swelling, thus prompting the patient to rub his eyes vigorously with his fingers. The eye rubbing further aggravated his discomfort. The patient was seen that day by his family physician, who treated him with antibiotic eyedrops. When the symptoms and signs showed only minimal resolution after three weeks of treatment, the patient was referred for ophthalmological con-



Figure 1: Straight arrows indicate discrete, mammular, deep corneal stromal infiltrates round partially degraded hairs. Curved arrow indicates keratic precipitate surrounding spider hair protruding posteriorly through Descemet's membrane into anterior chamber. Hairs not visible in photograph, but were better appreciable by actual clinical examination.

sultation. At that time, his visual acuity was 20/40 OD and 20/25 OS. Mild to moderate conjunctival redness and swelling were noted. By slit-lamp biomicroscopy multiple tarantula hairs were seen at all depths of both corneas. Some hairs were also noted to protrude through Descemet's membrane posteriorly into the anterior chamber. Hairs embedded in the corneal stroma were surrounded by focal, whitish, intrastromal infiltrates, while hairs protruding posteriorly into the anterior chamber were encapsulated with dense, 'mutton fat' inflammatory precipitates (Fig 1). A mild iritis was also present. The remainder of the ocular examination showed nothing remarkable.

As the spider hairs appeared deeply embedded in the corneas, we did not attempt to remove them. In order to reduce the existing inflammatory reaction in the anterior eye segment, topical corticosteroids were instilled in both eyes about 10 times each day during waking hours. A rapid decrease in the ocular inflammation was observed within 48 hours, and the corticosteroid eyedrops were tapered slowly over a period of three months. The embedded hairs gradually underwent resorption, and by 10 months none were visible. The visual acuity returned to 20/20 in both eyes, and the patient has remained symptom-free.

The irritative effects of tarantula hairs are thought to be mainly mechanical,^{1,2} though a toxic chemical or hypersensitivity phenomenon has not been ruled out. Cooke *et al.*¹ classified the hairs from Theraphosid spiders into four types. In small mammals, such as mice, a generalised inflammatory reaction from type IV hairs involving the respiratory tract may produce death from asphyxia. It is believed that type III hairs, which are long and thin with many sturdy barbs, are most likely to penetrate skin and cause severe urticaria in humans. *Brachypelma smithi*, a large colourful species native to Mexico and often sold in pet stores, has type III hairs. Eye injury from hairs have included keratitis, conjunctivitis, iritis, and putative chorioretinal scarring.¹⁴ We recommend that extreme caution be exercised during and after handling these spiders.

Patients suspected of having ocular injuries should be examined closely by slit-lamp biomicroscopy.

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- 1 Cooke JAL, Miller FH, Grover RW, Duffy JL. Urticaria caused by tarantula hairs. *Am J Trop Med Hyg* 1973; 22: 130-3.
- 2 Ratcliffe BC. A case of tarantula-induced papular dermatitis. *J Med Entomol* 1977; 13: 745-7.
- 3 Stulting RD, Hooper RJ, Cavanaugh HD. Ocular injury caused by tarantula hairs. *Am J Ophthalmol* 1983; 96: 118-9.
- 4 Hered RW, Spaulding AG, Sanitato JJ, Wander AH. Ophthalmia nodosa caused by tarantula hairs. *Ophthalmology* 1988; 95: 166-9.

Lactic acid and neovascularisation

SIR,—My opinion was that the *British Journal of Ophthalmology* is one of the best ophthalmological journals all over the world, but reading your editorial in the June issue¹ I am disappointed. In your editorial you cite my work² and then write: 'Later attempts to confirm this by demonstrating excess lactic acid in the vitreous of kittens and rats whose retinas has been rendered ischaemic were unsuccessful, and lactic acid seems to have been dropped.' This was the work of Gerke *et al.*³ and I am sorry that you have not read my answer to it.⁴ I reported that in cases of rubeosis iridis the lactic acid concentration of the aqueous humour is significantly increased, and stated that 'the findings of Gerke *et al.* (1976) prove that at the beginning of the proliferative phase of experimental fibroplasia the lactate content of the inner layers of the retina, i.e., of the least part of the investigated specimens, did not rise to a degree which could have significantly increased the lactate concentration of the whole vitreous-retina-choroid specimen'.

Since then I have summarised my work on ocular neovascularisations several times,^{5,6} and I know of some work of others confirming my findings. For example, Deem *et al.*⁷ and Cunha-Vaz¹⁰ have found that after a single injection of lactic acid into the vitreous there was an intensive endothelial proliferation or thymidine uptake – that is, the first signs of neovascularisation – in the retinal venules of experimental animals. I see that you have not met with these publications either.

I have not dropped the lactic acid and I am still working in it, and my results prove the following: (1) The lactic acid concentration of vascularising tissues is increased. (2) Increasing the lactic acid concentration of avascular tissues leads to vascularisation. (3) In cases of avascular swelling the lactic acid concentration is decreased. (4) L-lactate induces more intensive corneal vascularisation than D-lactate foreign to the organism. (5) Lactic acid in 10^{-3} M/l concentration stimulates the thymidine uptake and the proliferation of cultivated vascular endothelial cells in vitro.

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- 1 Smith R. Neovascularisation again. *Br J Ophthalmol* 1990; 74: 323.
- 2 Imre G. Studies on the mechanism of retinal neovascularisation: role of lactic acid. *Br J Ophthalmol* 1964; 48: 75-82.
- 3 Gerke E, Spitznas M, Brodde OE. The role of lactic acid in retinal neovascularization. *Graefes Arch Clin Exp Ophthalmol* 1976; 200: 79-84.
- 4 Imre G. The role of lactic acid in neovascularizations. *Graefes Arch Clin Exp Ophthalmol* 1977; 201: 263-6.
- 5 Imre G, Bögi J. Corneal vascularization. *Int Congr Symp Ser* 1981; 40: 233-5.
- 6 Imre G. The role of increased lactic acid concentrations in neovascularisations. *Acta Morphol Hung* 1984; 32: 97-103.
- 7 Imre G. Pathogenesis of proliferative retinopathy and rubeosis iridis of diabetics. In: Henkes H, ed. *Proceedings of the VIIth Congress of the European Society of Ophthalmology*. Helsinki: Yliopistopaino, 1985: 510-1.
- 8 Imre G. The role of lactic acid in the mechanism of neovascularization. *Doc Ophthalmol Proc Ser* 1987; 50: 511-6.
- 9 Deem CW, Futterman S, Kalina RE. Induction of endothelial cell proliferation in rat retinal venules by chemical and indirect physical trauma. *Invest Ophthalmol Vis Sci* 1974; 13: 580-5.
- 10 Cunha-Vaz J. Physiopathogenesis of retinitis proliferans and new vessel formation. In: François J, ed. *Blutkreislauf in der Uvea und im Sehnerven*. 5. Kong Europ Ges Ophthalmol Hamburg 1976. Stuttgart: Enke, 1978: 247-53.

** Many thanks to Professor Imre for his kind words about the *BJO*. As to the question of lactic acid and its role in neovascularisation, I am delighted to hear further details of this and also congratulate him for his determination in pursuing his researches. I am sorry he was disappointed that the editorial coverage was not complete, but the main function of this sort of editorial is to stimulate interest, and this seems to have been successful. I would be the first to admit that this type of editorial can never give complete coverage of a difficult subject like this. – ED, *BJO*.

Aqueous humour in insulin-dependent diabetic patients

SIR,—I read with much interest the article by Hayashi M, *et al.*¹ which reported on the decrease of aqueous humour formation in insulin-dependent diabetic patients, as measured by means of fluorophotometry. It is interesting to note that in 1965, by means of other methods (the suction cup of Rosengren

and Ericson and the recovery rate according to Okun), I and Diotallevi reported on the decrease of aqueous humour formation in diabetic patients.² No difference was found between diabetics with and without retinopathy. In contrast, we found that insulin treatment was able to restore aqueous humour formation to normal values in diabetic patients, provided retinopathy had not yet been observed. Our findings suggested that the rate of aqueous flow is influenced by insulin treatment in diabetic patients, at least in the initial stages of the disease.

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- 1 Hayashi M, Yablonski ME, Boxrud C, Fong N, Berger C, Iovanovic LJ. Decreased formation of aqueous humour in insulin-dependent diabetic patients. *Br J Ophthalmol* 1989; 73: 621-3.
- 2 Auricchio G, Diotallevi M. Beziehungen zwischen Insulinbehandlung und Kammerwasserproduktion bei Diabetikern. *Graefes Arch Clin Exp Ophthalmol* 1965; 168: 85-9.

SIR,—We appreciate Dr Auricchio's interest in and comments on our article. The suction cup method which Dr Auricchio used to measure aqueous humour formation is a pressure-dependent technique and has several inherent problems similar to those of tonography. We believe that fluorophotometry is a much more accurate method of investigating aqueous humour dynamics. However, we regret that we did not refer to Dr Auricchio's paper, which also found a decrease in aqueous humour formation in diabetic patients.

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Bacillus-induced endophthalmitis

SIR,—We regret that we incorrectly stated some antibiotic dosages in our article entitled 'Bacillus-induced endophthalmitis: new series of 10 cases and review of the literature' in the *BJO* 1990; 74: 26-9.

In Table II (p 27) the doses of 400 milligrams (mg) gentamicin (patients 5 and 8) are incorrect; the intravitreal dosage of gentamicin was 400 micrograms (μ g). The doses of clindamycin 1 gram (g) in patients 5 and 8 are also incorrect; the dose was 1 milligram (mg). Finally, the vancomycin 1 gram (g) dosage for patient 8 is incorrect; the dosage was 1 milligram (mg).

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BOOK REVIEWS

Primary Angle Closure Glaucoma. By R F Lowe and A S M Lim. Pp. 89. No price given. PG Publishing: Singapore. 1989.

This slim volume distils the experiences of two eminent ophthalmologists in the diagnosis and

management of angle closure glaucoma. The first eight chapters were written by Ron Lowe and reflect publications written by him on this subject dating from 1961. The remaining four chapters were written by Arther Lim and describe his operative and laser techniques in the treatment of this condition.

Dr Lowe's contribution covers pathophysiology, clinical types, examination, and management. Each chapter carries many words of wisdom, as is to be expected from an ophthalmologist who has spent much of his professional career studying angle closure glaucoma. Each chapter concludes with references for further reading.

Dr Lim's contribution describes methods for the surgical and laser treatment of angle closure. He covers iridectomy (though the illustrations for this appear to be the same as, but smaller than those which appeared in his book *Peripheral iridectomy*, also published by PG Publications), trabeculectomy, including complications, and concludes with a small section on combined cataract and glaucoma.

The authors do not identify a readership. This reviewer also found it difficult to see whom the book was directed towards. The book is a simple and didactic description of angle closure glaucoma. It would be covered in content by more general ophthalmological texts. The illustrations have substantially been published elsewhere. The text is too simple and without adequate references for the specialist student of glaucoma. If a coffee table existed for ophthalmology textbooks, this one could be on it, but it need not grace the bookshelf.

R HITCHINGS

Synopsis of Ophthalmology. 6th Edn. By Jack J Kanski. Pp 237. £14.95. Butterworth: Sevenoaks, Kent, 1989.

Aids to Ophthalmology. By P T Khaw, D S Hughes, S J Keightley, R F Walters, A R Elkington. Pp. 294. £8.95. Churchill Livingstone: Edinburgh, 1989.

These two books cover similar subject matter so are reviewed together. *Synopsis* is a completely revised 6th edition, the previous edition having been originally published in 1975. *Aids* is a new book from a group of authors from Southampton Eye Hospital. Similarities between the books include their size, both being easily transported paperbacks, and intended audiences, in both cases ophthalmologists in training approaching their postgraduate examinations. They are also similar in use of short note/list presentation rather than prose, and neither contains any illustrations or diagrams.

The subject matter in Kanski's book is a systematic review of the main aspects of clinical ophthalmology, the chapter titles including eyelids, orbit, lacrimal apparatus, etc. Khaw and co-authors cover this ground but add more basic science material including optics and pharmacology, a detailed chapter on visual standards and a dedicated chapter on medical ophthalmology. Neither book can really be faulted for the accuracy of information presented. Interestingly, both books cover the difficult topic of nystagmus, but neither quite reaches the standard of the masterly chapter in Bajandas and Klein's *Neuro-ophthalmology review manual* (Slack, 1988).

The print is much tighter on the pages of the book by Khaw and co-authors and is therefore a much more daunting prospect than the spacious and concise layout of Kanski's book. The quantity of information in *Aids* is also much greater, and it has much more the feel of

a condensed version of a textbook such as Newell's *Ophthalmology: principles and concepts* (Mosby, 1986). By contrast, Kanski sticks to mainstream clinical matters, which are covered in the neat way we have come to enjoy in his other books, including *Clinical ophthalmology* and *The eye in systemic disease*. The effect of these differences would be to make memorising the book by Khaw and co-authors a major challenge unless tackled with advanced examination preparations. Conversely, the moderately well read ophthalmologist in training could skim through *Synopsis* quite quickly and feel that new facts had been learnt on each page.

Both of these are good books and their authors are due great credit for the effort that their production must have involved. *Aids to ophthalmology* is packed with information and represents extremely good value for money. If I had to choose one to take on a desert island I would probably choose *Synopsis* because the delivery of information is so smooth.

Finally, I noticed that Duke-Elder's *System of ophthalmology* did not appear in the suggested reading at the end of *Aids*. I wonder if we could persuade the energetic authors of these two books to update the *System of ophthalmology*; this might once again mean that the definitive ophthalmic textbook came from the United Kingdom.

JOHN BRAZIER

Manual of Retinal Surgery. Edited by Andrew J Packer. Pp. 126. £29.95. Churchill Livingstone: Edinburgh. 1989.

This manual has been collected by a number of well-known American vitreoretinal surgeons. Nine chapters make up its contents, compressing much valuable information into a short book. It forms an admirable way for a junior ophthalmologist to get a quick overview of the principles of an approach to a patient with retinal detachment. As always in a book of this size there is a challenge to the contributors to limit their comments to what they consider to be the most important topics. It was nice to see the chapter by Chang emphasising the need for careful preoperative examination and charting, though it had not occurred to me that the nasal periphery of the retina is easier to examine after indentation of the temporal periphery has softened the eye. There are useful comments on the use of preoperative ultrasound, and the chapter on prophylaxis poses the questions but is not strong enough on providing clear-cut guidance on the author's views as to when treatment should be recommended. The controversial topic of pneumatic retinopexy is included, and there is a welcome, but relatively long contribution on the anaesthesia for surgery. The section on scleral buckling surgery is full of useful practical information, but sadly the principles governing non-drainage retinal detachment surgery are poorly explained and some of the indications for encirclement (the treatment of aphakic retinal detachment) are contentious. It would also have been better if the principles of peroperative injection of air and the operative sequence necessary for its correct use had been clearly elucidated.

The chapter on posterior segment vitrectomy by Abraham is particularly effective. The length of this section reflects the increasing use of vitrectomy in modern vitreoretinal surgery. The author cleverly manages to incorporate a substantial degree of sophistication in the techniques that he describes. These techniques are of course well beyond the capabilities of those for whom this manual is intended, but it

does at least expose them to the up-to-date assessment of current methods. The last chapter deals with complications and postoperative management. The author takes trouble to concentrate on fluid-gas exchange for post-operative problems arising from vitrectomy. It would perhaps have been appropriate for a discussion of the commonest complication of retinal surgery to have been included. This is of course failure of the procedure itself owing to an inadequately sealed retinal break, either due to a break that has been seen but inadequately closed or due to one that had been missed altogether.

Although it is rather expensive, the book is thoroughly enjoyable and informative, and I strongly recommend it to those entering ophthalmology who wish to become familiarised quickly with the principles of retinal surgery.

A CHIGNELL

The Eye in Systemic Disease. Eds. Daniel H Gold and Thomas A Weingeist. Pp 710. US\$87.50. Lippincott: Philadelphia, 1990.

This magnificent compendium comprises 20 parts and 230 chapters, each describing a different systemic disease. The number of chapters indicates the huge range of topics covered. They include chromosome disorders, infectious diseases, metabolic, skeletal, and skin disorders, as well as those diseases more familiar to ophthalmologists.

Each chapter is written by an expert with a personal interest in the subject and generally follows a similar format of introduction, systemic manifestations, ocular manifestations, and management. The section of systemic manifestations in each case is particularly useful for the ophthalmologist. This information is not found in any other ophthalmological textbook but has to be searched for in the appropriate medical encyclopedia. Overall the standard is very high, though some of the bibliography is old fashioned. This is more likely to be due to a defect of the time taken to produce such a book rather than the fault of the respective authors.

All multi-author books vary in the standard of individual chapters. Generally the information is relevant and succinct, and the illustrations, though limited by necessity, are informative. However, the management section of a few chapters is conspicuous by its absence or lack of information, particularly those on tuberculosis, histoplasmosis, and toxoplasmosis. Fortunately the chapters that seem weakest overall are the ones concerning problems most familiar to the ophthalmologist, for example, Graves' disease and herpetic disease: it is likely that the authors' brief in these cases was practically impossible to fulfil, and all ophthalmologists know how to obtain additional information on these subjects.

This book is great fun to dip into and succeeds in giving the ophthalmologist a comprehensive introduction to the systemic diseases associated with eye problems. It is a welcome addition to the ophthalmic literature and should be an essential part of all libraries and particularly those in general hospitals. The editors should be congratulated on their tremendous effort and proud of their appropriate dedication to Samson Weingeist and Paul Henkind, the latter a master of the importance of the eye in the diagnosis and management of systemic disease.

ELIZABETH GRAHAM

A Manual of Systematic Eyelid Surgery. 2nd Edn. By J R O Collin. Pp 166. £18.50. Churchill Livingstone: Edinburgh, 1989.

At a time when interest in ophthalmic plastic surgery is expanding and new operations seem to appear every month the updated second edition of this popular manual is a refreshing reminder of the well tried techniques. Richard Collin is a widely recognised teacher of ophthalmic plastic surgery, and the clear style and systematic approach reflect this. The concise step-by-step description of each operation is illustrated with excellent line diagrams by Mr Terry Tarrant, and flow charts simplify the decisions. Discussion is kept to a minimum, but this is balanced by suggestions for further reading.

Several changes have enhanced the value of the second edition. A new chapter on lacrimal surgery has been contributed by Mr Dick Welham. The revised approach to eyelid reconstruction includes new flow charts for posterior lamellar defects (symblepharon) and full thickness defects; the uses of local transposed flaps, omitted from the first edition, are described, and the principles of eyelid tumour management are discussed in more detail. A separate chapter is given to an expanded section on eyelid injuries which includes medial canthal tendon injuries and traumatic ptosis. Other additions to this edition include the dermofat graft and new flow charts for the management of thyroid eye disease and myogenic ptosis.

Successful surgery depends on translating the principles into practice – essentially, recognising the anatomy at operation. Experienced ophthalmic plastic surgeons will have no difficulty in following the diagrams accurately. Those with less experience may need help with some of the operations described. However, the particular appeal of this manual will be to general ophthalmic and plastic surgeons and those starting ophthalmic plastic surgery as a special interest. It is concise, comprehensive (an answer is offered for almost every circumstance), and very good value for money. Every medical library should have a copy, but most surgeons who operate on eyelids will want one of their own. Highly recommended.

AG TYERS

NOTES

Association for Eye Research

The Association will hold its 32nd Annual Meeting on 3–7 July 1991 at Århus, Denmark. Details from Professor N Ehlers, Department of Ophthalmology, Århus University Hospital, DK-8000 Århus C, Denmark.

£100 Award. The Association will award a Publication Prize of £100 sterling for the best paper on eye research published in the 12 months up to the meeting whose principal author (member or non-member) is under 35 at the time of publication. Closing date 1 May 1991. Details from Dr N J van Haeringen, General Secretary AER, Netherlands Ophthalmic Research Institute, PO Box 12141, 1100 AC Amsterdam, The Netherlands.

Vision research course

The 12th annual course of the National Eye Institute, USA, will be on 'Clinical vision research: epidemiologic and biostatistical approaches' on 24–27 April 1991 at Longboat Key, Florida. Details from Christine Stewart, Maite Mavila, Stewart International Ltd, 87 Boylston Street, Brookline, MA 02146, USA. Tel: 617 738–1575. Fax: 617 738–8215.

Polish congress

The First World Congress of Medical Polonia (doctors of Polish extraction) will be held on 19–23 June 1991 at Czeszochowa, Poland. Details from: Krzysztof Muskalski, MD, 1st World Congress of Medical Polonia, Dr Rydygier's Surgical Hospital, ul Mirowska 25, 42–200 Czeszochowa, Poland.

Korea conference

The 4th International Cataract, Implant, Microsurgical and Refractive Keratoplasty (ICIMRK) meeting will be held at Seoul, Korea, on 8–10 May 1991. Further information from: Jae Ho Kim, MD, Department of Ophthalmology, Kangnam St. Mary's Hospital, Catholic University Medical College, 505 Banpo-dong, Seocho-ku, Seoul 137–040, Korea. (Tel: 82–2–593–5141, 6121 (ext 1335). Fax: 82–2–533–6718.)

German Ophthalmological Society

The German Ophthalmological Society will sponsor an International Symposium in Bonn-Köln on 19 to 21 September 1991. The symposium will cover both clinical and research aspects of ocular infections and will include a basic sciences course. Further information from A A Bialasiewicz, MD, University Eye Hospital Bonn, Sigmund Freud Str 25, 53 Bonn 1, West Germany.

Endogenous ocular inflammations

The University Eye Clinic of Jena, Germany, will hold an international symposium on 'Endogenous ocular inflammations – Uveitis '91' on 2–6 October 1991 in Weimar/Thuringia sponsored by the Thuringian Ophthalmological Society. Further information from: Professor S Klein, Chairman, Department of Ophthalmology, Bachstrasse 18, D-06900 Jena, Germany. (Tel: Jena 8223270.)

David Cole travel fellowship

The David Cole travel fellowship, instituted by Merck Sharp and Dohme in memory of Professor David Cole, will assist a visit to a hospital or research centre during the academic year starting 1 October 1991. The award will be equivalent to £2000. Its purpose is to enable the successful applicant to gain experience and knowledge in pursuit of a specific project related to glaucoma.

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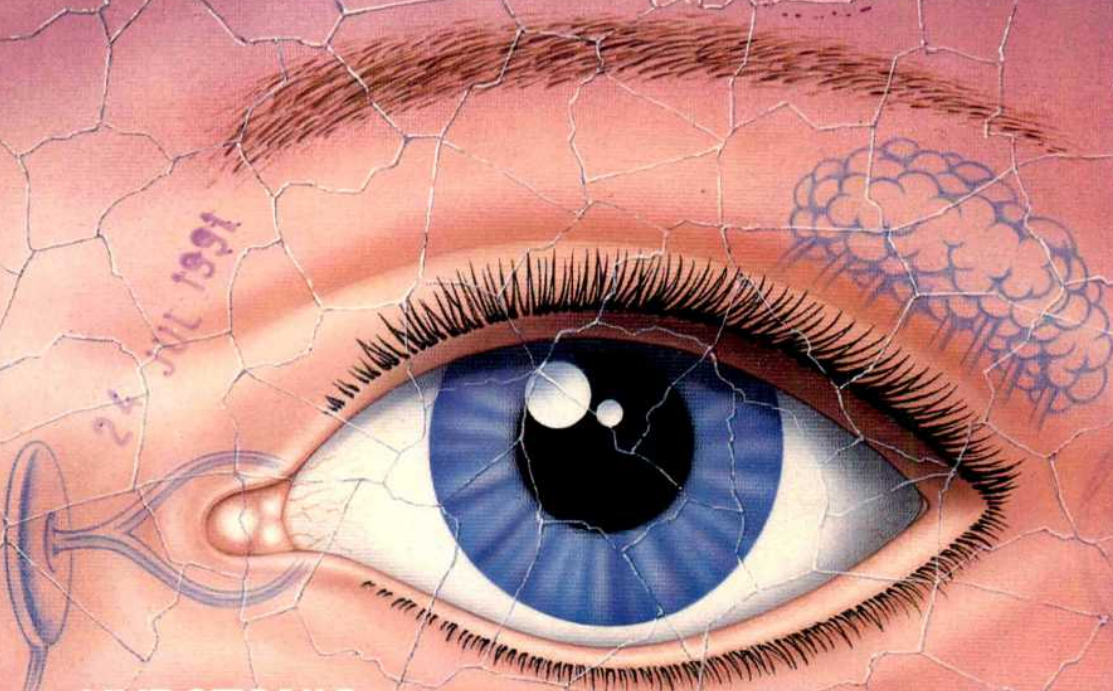


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1. Izman, E. *et al.*, Am J Ophthalmol 1982; 94 (3): 318-327. 2. Rakofsky S.I. *et al.*, Ophthalmology 1989; 96 (1): 8-11. 3. Wandel, T. *et al.*, Am J Ophthalmol 1986; 101: 298-304.



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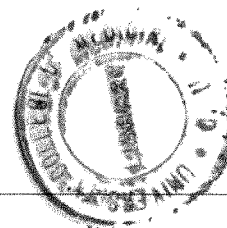
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BRITISH JOURNAL OF OPHTHALMOLOGY



Editorial

Excimer laser for anterior cornea

The paper by Gartry, Kerr Muir, and Marshall in this number of the journal is the first publication of the results of treating pathological conditions of the anterior cornea with the excimer laser. The authors have shown convincingly that such conditions can be treated safely and effectively, and they are to be congratulated on their thoroughly planned and conscientiously conducted research. However, cases suitable for this treatment are relatively few and would hardly justify the substantial investment which is being directed towards the development of the excimer laser for ophthalmic use. The drive behind this development is the possibility of using the excimer laser for photorefractive keratoplasty. That the excimer laser is an effective and above all safe method for refractive surgery remains to be proved, and it is to be hoped that the long-term, carefully monitored, prospective studies which are needed will not be pre-empted by its premature wider use for photorefractive keratoplasty. Nevertheless its potential application in refractive surgery raises important issues which ophthalmologists should consider, and it would seem desirable that the debate should take place before rather than after the method becomes widely available.

Important economic considerations may influence priorities for the allocation of health care resources in Britain, particularly with the introduction of the internal market in the National Health Service. For example, how should ophthalmologists respond to pressures from health service managers to engage in work which might generate income though possibly at the expense of ophthalmological skill being directed to other needs. Should this technology be available to ophthalmologists only, or should other professionals engage in its use? This matter is already a live issue in the United States.

The College of Ophthalmologists should be encouraged to take the lead in addressing these matters so that ophthalmologists can be helped to form their own opinions and appropriate advice can be given to those bodies who look to the college for responsible and considered professional advice. Failure to act now runs the risk of the inevitable debate degenerating into an unhelpful contest dominated by those whose opinions are dictated either by self-righteousness or by self-interest.

NOEL RICE

ORIGINAL ARTICLES

Excimer laser treatment of corneal surface pathology: a laboratory and clinical study

David Gartry, Malcolm Kerr Muir, John Marshall

Abstract

The argon fluoride excimer laser emits radiation in the far ultraviolet part of the electromagnetic spectrum (193 nm). Each photon has high individual energy. Exposure of materials or tissues with peak absorption around 193 nm results in removal of surface layers (photoablation) with extremely high precision and minimal damage to non-irradiated areas. This precision is confirmed in a series of experiments on cadaver eyes and the treatment of 25 eyes with anterior corneal disease (follow-up 6 to 30 months). Multiple zone excimer laser superficial keratectomy is considered the treatment of choice for rough, painful corneal surfaces. All patients in this group were pain-free postoperatively. Where good visual potential exists, ablation of a single axial zone is recommended and results in improved visual acuity and reduction of glare. A hyperopic shift was noted in this group.

The potential of excimer lasers in ophthalmic surgery was first suggested in 1983¹ following their successful industrial application in etching highly precise patterns into plastics.¹⁻⁵ A distinct advantage of argon fluoride excimer laser radiation (193 nm) is that there is no significant damage beyond exposed areas. Ultrastructural examination of corneal excisions in animal models confirmed that these could be produced with a very high degree of accuracy and control. Damage to adjacent unexposed tissue was limited to 300 nm beyond the boundary of the zone of ablation.⁶⁻⁹ In non-perforating excisions of varying depths endothelial damage was noted only when the base of the excision was within 40 µm of Descemet's membrane, which is similar to but less extensive than diamond knife incisions.^{6, 10, 11} Furthermore, excisions can be controlled precisely, in terms of uniformity along the length of a single cut, reproducibility between cuts, and in anticipated cut depth (accuracy $\pm 3\%$, diamond knife incisions $\pm 12\%$). The first clinical application was therefore the correction of astigmatism with T-cut excisions.¹²

The nature of corneal damage induced by excimer radiation at 193 nm is unique, because it results from an extremely high photon energy and high peak power. At this wavelength each photon has an energy of 6.4 electron volts, and, as this exceeds the binding voltage of carbon-carbon bonds, a single absorbed photon may lead

to bond breakdown.¹³ Ultraviolet radiation in this spectral domain does not propagate well in air, and at any biological interface the photons are virtually all absorbed within a few microns of the surface. Thus, with each laser pulse a layer of tissue only a few molecules thick will be ablated from the surface. Tissue damage induced by other clinical lasers is achieved by concentrating laser energy into a focused point. However, the excimer laser beam has a large cross sectional area, and since every photon in the beam has the potential to produce tissue change the entire cross section can be utilised. The 1 cm by 2 cm rectangular profile is adjusted by cylindrical quartz lenses, and the resultant square beam profile becomes circular by passing the emergent beam through an aperture.⁹ This facility to photoablate large areas of cornea permits selective removal of tissue to induce a refractive change (photorefractive keratectomy - PRK).^{9, 14-18}

For PRK and superficial keratectomy to become accepted in clinical practice an understanding of the nature and quality of wound healing is essential. Complete epithelial wound healing is necessary to re-establish the outer osmotic barrier of the cornea and optical brilliance. Studies have been undertaken to assess latency of wound healing, epithelial migration and adhesion properties, and the presence or absence of hyperplasia.¹⁹ Stromal wound healing has been examined in relation to loss or disturbance of transparency, keratocyte infiltration, and scar formation.^{14, 16, 20} Endothelium has been assessed in relation to potential cell loss or long-term population changes.^{19, 21} Finally the putative mutagenic effects of ultraviolet radiation on the cornea have been assessed by both unscheduled DNA repair and tissue culture, coupled with enzyme poisoning techniques.^{22, 23} None of these studies has highlighted areas of concern that would preclude the beginning of clinical trials with the excimer laser at 193 nm (Sloney D, personal communication).

In February 1988, on the basis of laboratory data, ethical committee approval was given to treat overt corneal lesions with the excimer laser. The aim of this study was to determine whether the laser could be used for wide area ablations to remove opacities and produce an optically smooth surface. Since photoablation occurs across the entire area exposed, with repeated pulses the original surface contour will be reproduced in the base of the ablated disc. It was necessary therefore to devise a means of smooth-

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ing an uneven surface. The simplest method of achieving this was to apply a liquid with approximately the same ablation properties as the cornea. The surface tension of the liquid would ensure that any surface irregularities would be negated. If irregularities in the corneal surface had a different ablation rate from that of the surrounding tissue – for example, the calcium deposits in band keratopathy – it would be necessary to shield underlying tissue with a liquid while the crystalline peaks underwent ablation.

This paper describes the use of the excimer laser for the production of large-area, optically smooth corneal surfaces in the laboratory and in the clinic.

Materials and methods

After ethical committee approval all clinical trials were carried out in the Department of Ophthalmology at St Thomas's Hospital, London. A Summit Technology UV200 excimer laser was used with spectral emission at 193 nm. The pulse energy resulted in a radiant exposure of 180 mJ/cm²; the pulse frequency was fixed at 10 Hz and tissue removed per pulse was 0.24 µm. The beam configuration was circular in cross section, and a number of fixed beam diameters were used between 1 and 4 mm.

EXCIMER LASER PATTERN ABLATION IN CADAVER EYES

(1) The aim of this experiment was to create an irregular surface in cadaver corneas and then to determine whether the excimer laser could smooth these irregular surfaces. Donor eyes were used within 16 hours of death and secured in a Tudor Thomas stand. Ocular rigidity was maintained by injecting normal saline into the vitreous through the pars plana. After removal of the epithelium with a hockey end blade the globe was placed directly beneath the laser aperture and the helium-neon aiming beams focused on the centre of the cornea. An area of stroma was masked by placing a piece of bent wire on the corneal surface in the path of the beam. Fifty pulses of laser energy were then directed on to the partially occluded corneal surface with a 3 mm diameter beam. This resulted in excavation of the stromal surface in areas not shielded by the wire. In areas beneath the wire, ridges of original tissue remained.

The next objective was to remove the induced pattern with the laser to restore a smooth surface across the entire ablated zone. The wire was removed and the excavated areas 'masked' with 1% or 2% hydroxypropylmethylcellulose (HPMC) or polyvinyl alcohol to prevent their further ablation. These tear substitutes have a high water content and were assumed to have similar ablation rates to corneal stroma.

(2) In this experiment the excimer laser was used to create a cylindrical excavation 1 mm in diameter and 100 µm deep. The beam diameter was then increased to 3 mm, the ablated cylinder filled with 1% HPMC, and the surrounding stromal surface carefully dried. Ablation of the stroma was continued until the surrounding

stroma had been ablated to the same depth as the original cylinder. In practice this process was monitored by changes in tissue fluorescence to be described in the results.

EXCIMER LASER SMOOTHING OF SURGICAL LAMELLAR KERATECTOMY BEDS

This experiment was designed to assess the potential of the excimer laser in combination with masking agents to smooth irregular corneal surfaces. A series of surgical lamellar keratectomies was performed on donor eyes. The initial incision was made with a disposable 6 mm trephine, and the lamellar dissection was done with a steel blade and Paufigue's knives, beginning at the base of the trephine cut. HPMC was applied to the keratectomy base and its amount and distribution adjusted, while multiple overlapping ablation zones were produced until the base was smooth.

HISTOPATHOLOGY

After laser exposure a 5 mm penetrating incision into the posterior globe was made and the eyes were immersed in fixative. The initial fixative used was 2.5% glutaraldehyde buffered in 1 M sodium cacodylate with 10 g/l calcium chloride at a final pH of 7.4. After 24 hours the corneas were prepared for light microscopy (LM) and electron microscopy (EM). Those for scanning EM were postfixed overnight in 2% osmium tetroxide buffered in 0.1 M sodium cacodylate, dehydrated through a series of ascending concentrations of acetone, and critical-point dried. Dried samples were sputter-coated with a 30 nm layer of gold before examination in a Hitachi 520 scanning electron microscope (SEM). For transmission electron microscopy (TEM) specimens were postfixed for only one hour in the osmium tetroxide solution described above, dehydrated in alcohol, and then embedded in Araldite (CY212) via epoxypropane. Sections were cut at 1 µm on glass knives for LM and on diamond knives for EM and mounted on 200 mesh copper grids, stained with uranyl acetate and lead citrate before examination in an ABI 801 transmission electron microscope.

TREATMENT OF BAND KERATOPATHY AND ALLIED SUPERFICIAL PATHOLOGIES

Twenty five patients underwent excimer laser superficial keratectomy to remove band keratopathy or to smooth roughened corneal surfaces arising from other pathology (see tables). Amethocaine 1% was instilled, a speculum inserted, and the patient taught to fixate the centre of a ring of fibreoptic lights located around the laser aperture. A beam diameter was selected to match the areas to be treated, and in some cases the size of the beam was reselected at different stages in the procedure. The effects of photoablation were assessed with the integral binocular operating microscope positioned alongside the laser aperture. Once steady fixation was achieved, the masking liquid was applied to the corneal surface and photoablation started. During the process the surgeon could vary the

site of ablation by making small movements of the patient's head. After the procedure, which lasted about 15 minutes, a mydriatic (homatropine 2% eye drops) and antibiotic (chloramphenicol 1% eye ointment) were instilled and the eye padded for 24 hours. Follow-up was daily for the first week, weekly for one month, three monthly for two further visits, and then six monthly. For the first month chloramphenicol 0.5% eye drops were used four times a day.

The surface characteristics of selected patients were examined and recorded with a prototype photokeratoscope.²⁴ In addition, while it was impossible in most cases to comment on the preoperative status of the corneal endothelium owing to superficial opacification, it was examined postoperatively at intervals via specular reflection with the slit-lamp. Refraction was carried out where possible.

Although the morphology of band keratopathy varies, we subdivided the patients into two broad categories. The first had rough, craggy deposits with varying degrees of discomfort, the second, smooth even deposits with little or no discomfort.

Two treatment regimens were undertaken. Either a single 4 mm diameter zone or a series of partially overlapping 4 mm diameter zones was ablated. The single area technique was most commonly used for smooth bands which caused impaired vision and glare and the multiple zone technique for rough, painful bands. The noise associated with laser pulses (10 Hz) was demonstrated to the patients prior to the procedure, and they were warned to expect a faint smell of burning during treatment (see below).

Results

EXCIMER LASER PATTERN ABLATION IN CADAVER EYES

(1) The bas relief pattern produced on the cornea by shielding the underlying stroma by bent wire was best demonstrated by SEM (Figs 1A, 2A). The smoothness of the ablated surface was comparable to Bowman's layer on the non-ablated ridges, and the stromal architecture was obscured by a continuous membrane-like structure. The ridges, noted to have smooth perpendicular walls, were successfully ablated to produce a homogeneous, optically smooth surface (Fig 1B). In some specimens the ablation to produce the pattern and the subsequent smoothing ablation were not coincident. This resulted in a small peripheral annulus in which the ridges could still be seen (Figs 1B, 2B).

The most suitable masking liquid was 1% HPMC, since it was easy to apply and remove and filled the declivities between surface irregularities. HPMC fluoresced a bright blue when irradiated and corneal stroma a dark blue-black. There was thus a clear indication of the three dimensional geometry of stroma undergoing ablation. When 1% HPMC flooded the surface, an even bright blue fluorescence was noted across the entire target area with each pulse. As the masking agent was ablated, corneal stromal irregularities projected through the surface of the HPMC and were ablated, as dark blue,

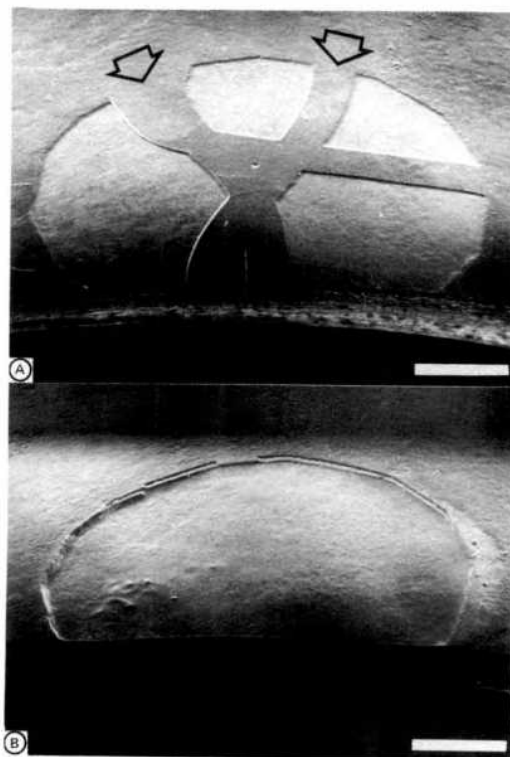


Figure 1 Scanning electron micrographs of the surface of human donor corneas after excimer laser irradiation. (A) The pattern created by shielding stroma with a piece of bent wire during irradiation is shown. The ablated surface adjacent to the non-ablated ridges (arrowed) is smooth and the ridges themselves are sharply demarcated. The sides of these ridges are perpendicular as is the edge of the ablated zone. (B) A pattern similar to that in (A) has now been ablated leaving an almost totally smooth surface. A small peripheral annulus indicates that there has been a slight shift in the position of the eye prior to the final smoothing ablation. (Bar=500 μ m.)

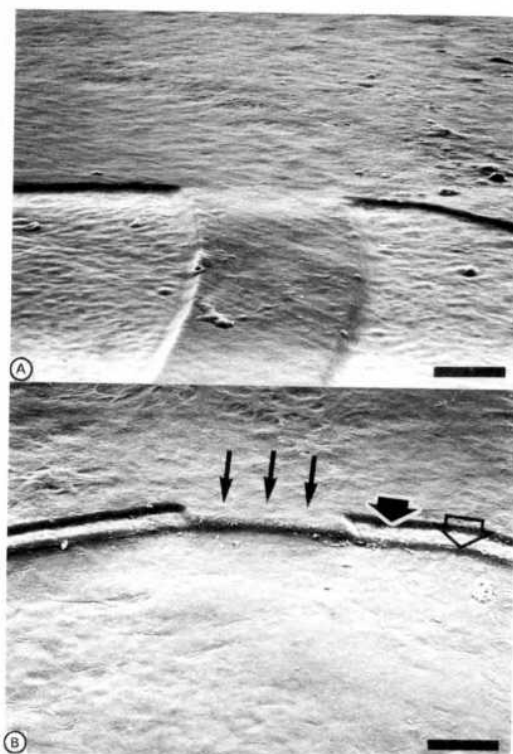


Figure 2 High power scanning electron micrographs of the ridges created and removed by excimer laser irradiation. (A) Shows the magnitude and edge quality of the ridge seen in Fig 1. (B) Shows the residual portion of a ridge (fine arrows) after a smoothing procedure. The ablation depth involved in generating the initial pattern (closed arrow) and that involving its removal (open arrow) can be clearly distinguished as a result of displacement of the globe between the two procedures. (Bar=100 μ m.)



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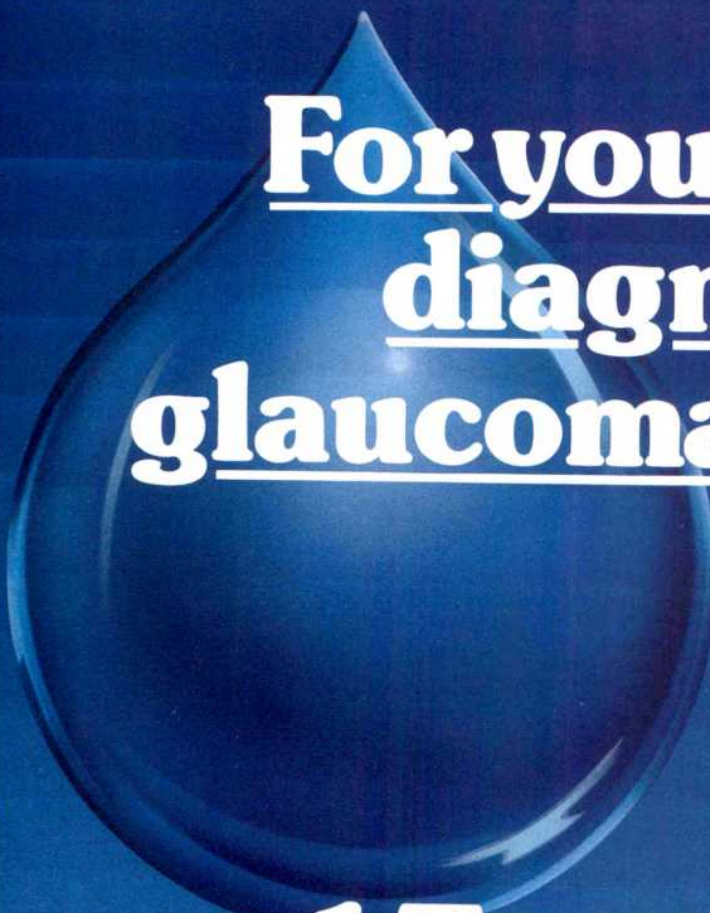
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References

1. Maclure G.M. et al. 3rd Congress of European Glaucoma Society, 1988.
2. Kitazawa, Y. et al. Acta XXIV International Congress of Ophthalmology, 1983. P. Henkind (Ed), Lippincott, Philadelphia.
3. Hugues, F.C. et al. J. Fr. Ophthalmol. 1987; **10**, 8/9, 485-490.
4. Negishi, C. Acta Soc. Ophthalmol. Jpn. 1982; **85**, 57-66.
5. Scoville, B. et al. American Journal of Ophthalmology, 1988; **105**, No.2, 150-154.

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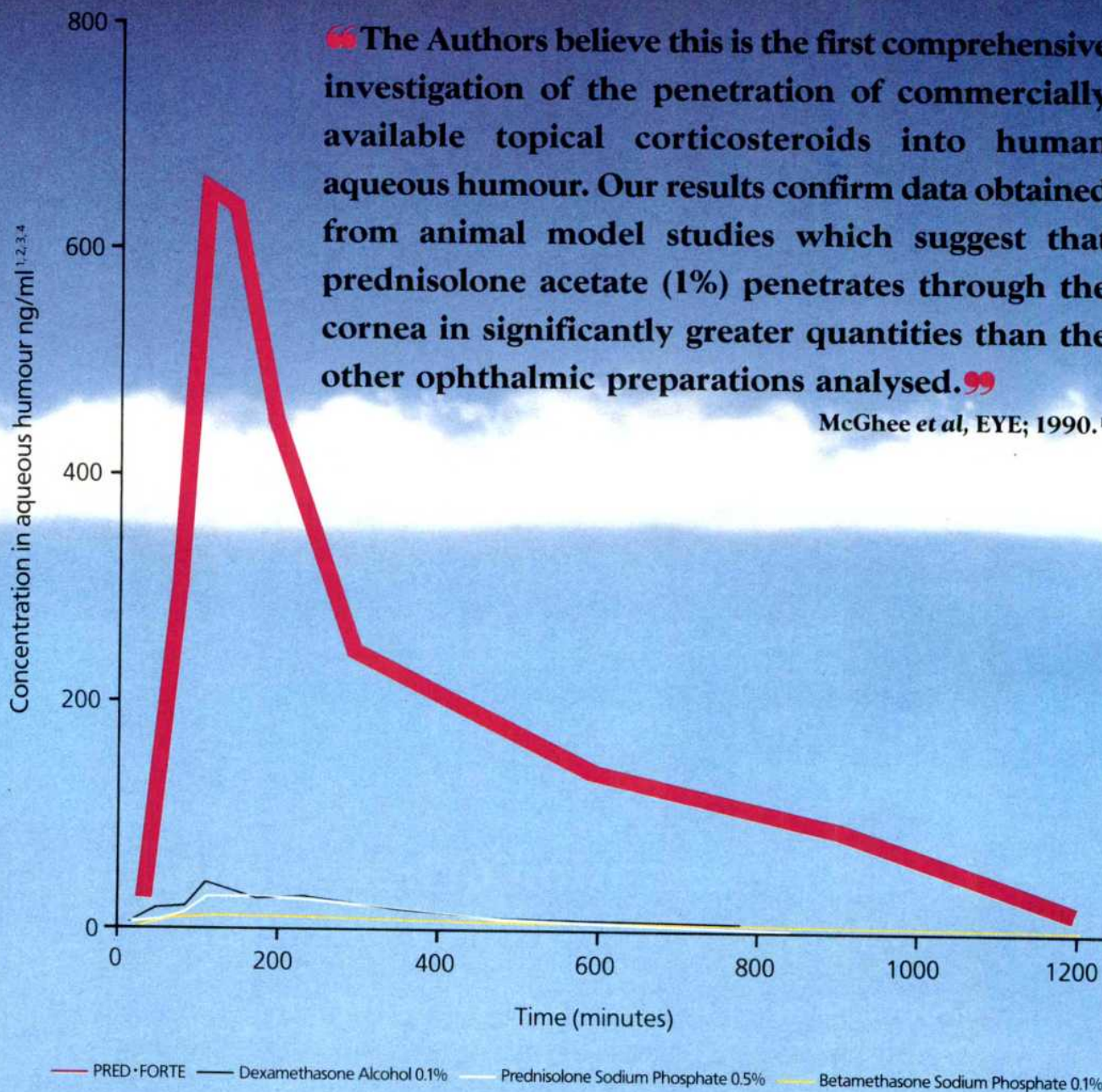


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CLINICAL UPDATE



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References 1. Penetration of Synthetic Corticosteroids into Human Aqueous Humour. Watson D.J., Noble M.J., Dutton N., Midgley J., Healey T., Arch Ophthalmol 106, May 1988, 686-687. 3. Comparative Studies of the Penetration of Synthetic Corticosteroids into the Human Eye by GC-NICIMS. Midgley J.M., McGhee C.N.J., Watson D.G., Noble M.J., Healey T., Dutton G.N., J Pharm Pharmacol 1988 Dec; 4(Suppl): 16P. 4. Penetration of Topically Applied Prednisolone Sodium Phosphate into Human Aqueous Humour. McGhee C.N.J., Noble M.J., Watson D.G., Dutton G.N., Fern A.J., Healey T.N., Midgley J.N., Eye 1989, 3, 463-467.

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almost black, 'islands' within the bright blue HPMC fluorescence. As ablation proceeded, so the pattern and surrounding masking agent were removed until a common depth was reached, at which point HPMC once again spread throughout the 3 mm zone, indicated by homogeneous bright blue fluorescence. Further ablation beyond the original depth of 10–12 µm removed the little remaining HPMC, and the entire area appeared dark blue-black, with each pulse confirming that the pattern had been completely removed. If further pulses were applied, then the 3 mm zone of ablation was uniformly increased in depth (Fig 1B). With relief patterns in excess of 30 µm it was more difficult to achieve uniform smoothness because of a meniscus effect where the masking agent met the vertical sides of the pillars of non-ablated tissue. It was found that blotting the edges with cellulose (Weck-cell) sponges reduced this effect.

(2) In this experiment a 1 mm diameter cylinder of corneal stroma was ablated and filled with HPMC. On ablating the area around the cylinder there was differential fluorescence – the central spot (HPMC) bright blue, the surrounding stroma dark blue-black. The end-point was reached when the blue spot disappeared and the entire area of ablation became uniformly black – that is, the surrounding stroma had been ablated to exactly the same depth as that of the original cylinder. The number of pulses required for these two processes was similar.

EXCIMER LASER SMOOTHING OF SURGICAL LAMELLAR KERATECTOMY BEDS

Scanning electron microscopy of the base and walls of a surgical lamellar keratectomy showed surfaces with a marked degree of destruction and dissociation of cellular and extracellular components. The walls of such sites showed stratification with alternate layers of compression and shearing. There was an annulus in which epithelial cells were wiped off Bowman's layer because the surface tissue was displaced and compressed against the barrel of the trephine and debrided as the trephine rotated. The floor never displayed a cleavage plane and always consisted of ripped, torn lamellae and displaced ruptured keratocytes (Fig 3A).

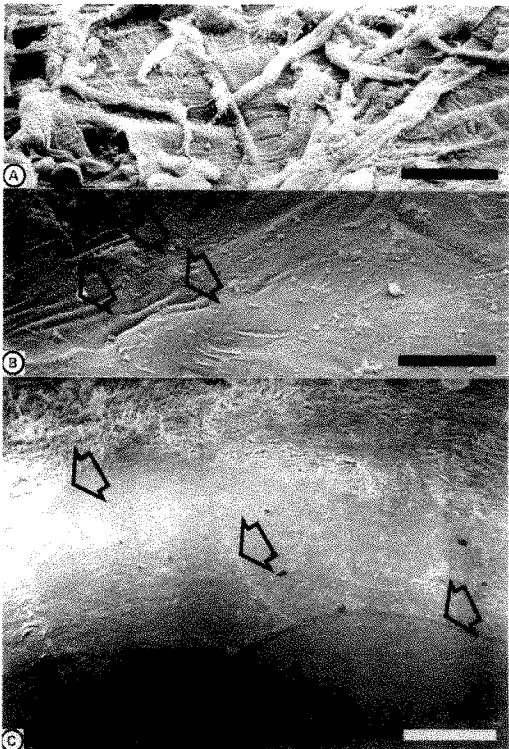


Figure 3 Scanning electron micrographs of the corneal surface subsequent to (A) surgical lamellar keratectomy; (B) and (C) excimer laser irradiation. (A) The bed of a lamellar keratectomy showing rough, disorganised and torn tissue. (Bar=50 µm.) (B) A surgical lamellar keratectomy bed smoothed by excimer laser irradiation. The surface has a confluent membrane-like quality seen as wrinkles and folds produced during preparation for scanning electron microscopy. (Bar=50 µm.) (C) A lamellar keratectomy bed smoothed by application of multiple overlapping zones of excimer laser radiation. The slight discontinuities between different zones are seen as variations in ablation depth and defined by arcuate boundaries (arrowed). (Bar=500 µm.)

The most appropriate method of smoothing lamellar beds was achieved by frequently applying small amounts of masking agent and constantly readjusting local distribution with cellulose (Weck-cell) sponges. This enabled removal of multiple small surface perturbations without unnecessary removal of deeper stroma. The resultant surface was smooth, with some wrinkles and folds suggesting a surface membrane (Fig 3B). Multiple overlapping ablation zones were used to smooth the entire keratectomy base (Fig 3C). Zones already smoothed

Table 1 Rough band keratopathy treated by several overlapping ablation zones

No.	Sex	Age	Band type	Aetiology	Preop. symptoms	VA	Postop. symptoms	Follow-up		
								VA	Time (months)	Comment
1	F	49	Rough surface very irregular	Increased serum Ca ⁺⁺	Pain, photophobia decreased VA	6/36	Asymptomatic	6/12	30	Band recurred after 18 months
2	M	45	Rough, very irregular	Trauma	Pain	PL	Asymptomatic	PL	30	Stable
3	M	50	Rough, raised, thick band	Trauma	Pain	NPL	Asymptomatic	NPL	30	Stable
4	M	34	Rough, irregular disrupted ant. seg	High myope, failed retinal detachment surgery	Irritable, red, pain on blinking	PL	Asymptomatic, pleased with cosmesis	PL	14	Stable
5	F	66	Central, proud Ca ⁺⁺ plaque	Keratitis due to herpes simplex virus	Pain, decreased VA	CF	Asymptomatic, (occasional ache)	6/36	14	Stable
6	F	72	Classic band	Herpes zoster	Pain, epiphora decreased VA	6/24	Asymptomatic	6/18	12	Stable
7	F	33	Islands of Ca ⁺⁺ (previous edetic acid treatment)	Uveitis (childhood)	Poor cosmesis, minimal discomfort	NPL	Unchanged	NPL	10	Highly mobile eye during treatment (surgery abandoned)
8	F	78	Central Ca ⁺⁺ area and diffuse Ca ⁺⁺ surround	HSV keratitis	Pain, epiphora, decreased VA	CF	Asymptomatic, slight increase in VA	4/60	10	Stable

VA=visual acuity. (N) PL=(no) perception of light. CF=counting fingers. HSV=herpes simplex virus.

Figure 4 Case 1. Rough band keratopathy. (A) Preoperative appearance. Extensive calcium deposition is present producing a grossly uneven surface. (B) Immediate postoperative appearance. The majority of the calcium has been ablated, leaving a smooth surface. (C) Appearance five months after treatment with the excimer laser. (D) Appearance 18 months after ablation. Treated areas remain clear, but recurrence of band keratopathy has resulted in some loss of corneal transparency.



Figure 4A.

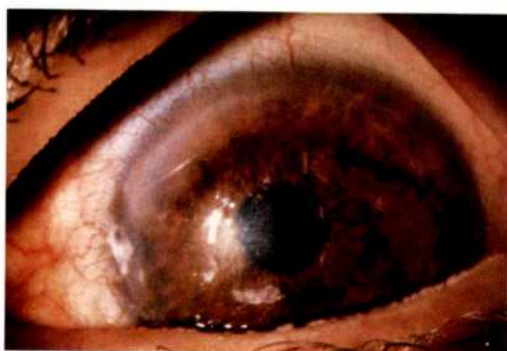


Figure 4B.



Figure 4C.



Figure 4D.

were masked with HPMC to avoid unnecessary ablation. This technique was important in establishing criteria for treating large areas of stroma in the subsequent clinical cases.

TREATMENT OF BAND KERATOPATHY AND OTHER SUPERFICIAL CORNEAL PATHOLOGY

Twenty-five patients have had excimer laser treatment of band keratopathy or superficial corneal pathology since February 1988 (Tables 1–5). The six cases reported here in detail represent the spectrum of disease and illustrate different techniques of band removal with the excimer laser.

GROUP I. ROUGH SYMPTOMATIC (UNCOMFORTABLE) BAND KERATOPATHY

Case 1

A 49-year-old female with systemic lupus erythematosus requiring renal dialysis since 1981 had a parathyroidectomy in 1984 for primary hyperparathyroidism. Her left eye had been painful

since 1974 and was treated with artificial tears. In 1987 she had removal of band keratopathy with edetic acid (EDTA). In spite of this she still had severe pain in the left eye, aggravated by blinking, which disrupted sleep. There was extensive irregular, thickened band keratopathy with a visual acuity of 6/36. Islands of calcium protruded through unstable epithelium (Fig 4A). The right eye was normal.

In February 1988 she became the first sighted patient to undergo excimer laser superficial keratectomy (ELSK). She had multiple overlapping zones located in the central 6 mm of the cornea (Fig 4B). Approximately 300–400 pulses were delivered to each site of ablation. The procedure was pain-free. One hour later, however, she complained of some discomfort, which resolved over 36 hours when the cornea had re-epithelialised. One week later she was asymptomatic. At this stage the area of photoablation was smooth, with minimal central thinning and a faint anterior stromal haze. The acuity was 6/24 improving to 6/12 with pinhole. At five months there was early recurrence of band keratopathy (Fig 4C). By 18 months it began to cause

Figure 5 Case 2. Rough band keratopathy. (A) Preoperative appearance showing gross irregularity of the corneal surface and opacification. A large central calcium plaque is evident. (B) Postoperative appearance at one week. The large calcium deposit has been completely ablated. The patient remains asymptomatic after 18 months.



Figure 5A

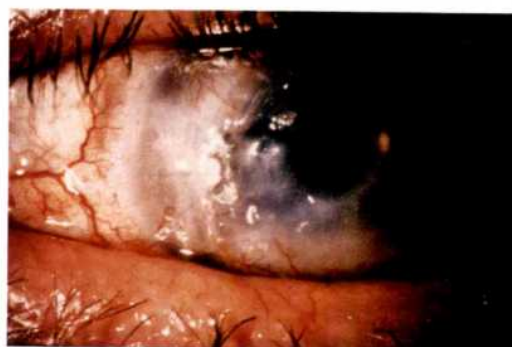


Figure 5B

Figure 6 Case 3. Even, diffuse band keratopathy. (A) Appearance one year after excimer laser ablation of a single, 'on-axis' zone. The photograph was taken slightly eccentrically in order to highlight the enhanced transparency of the ablated zone against the iris. (B) Photokeratoscopic image preoperatively. (C) Appearance one month following central ablation.

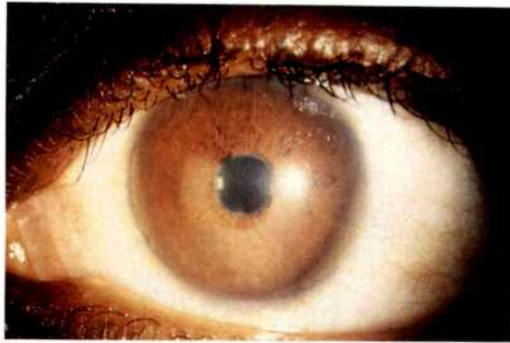


Figure 6A.

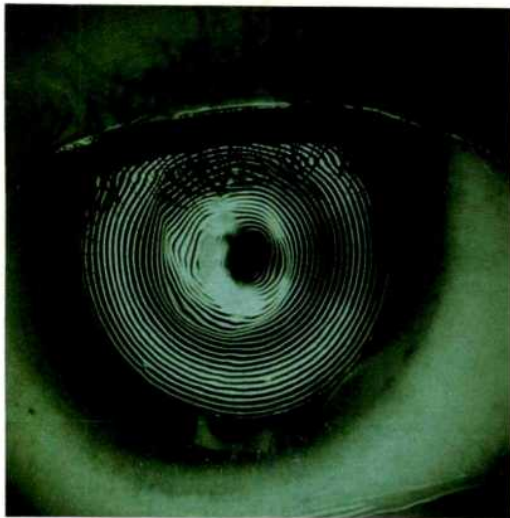


Figure 6B.

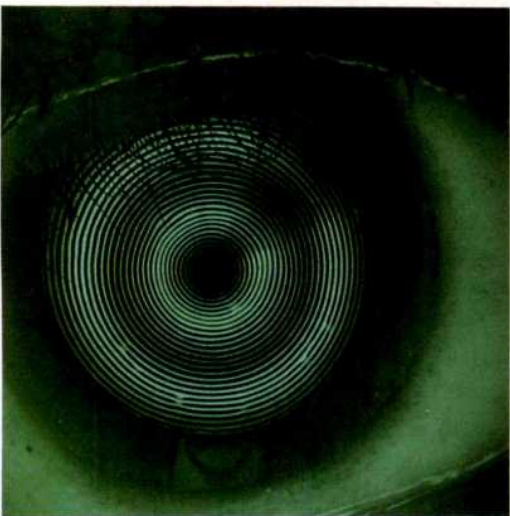


Figure 6C.

discomfort. A small central epithelial erosion and faint central stromal haze were noted at this time, with the zone of ablation remaining markedly clearer than the surrounding area (Fig 4D).

Case 2

A 45-year-old male had sustained blunt trauma to his left eye at the age of 24. Band keratopathy, cataract, and glaucoma had resulted, and he underwent a series of procedures between 1984 and 1987 – corneal graft, cataract extraction with lens implant, two trabeculectomies and drainage

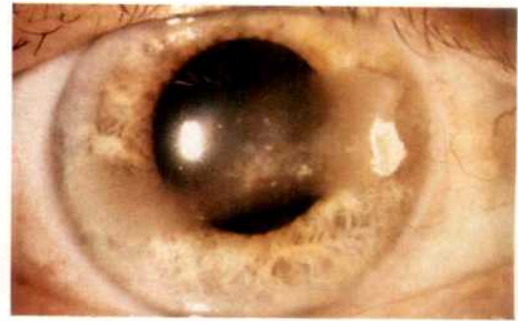


Figure 7A.

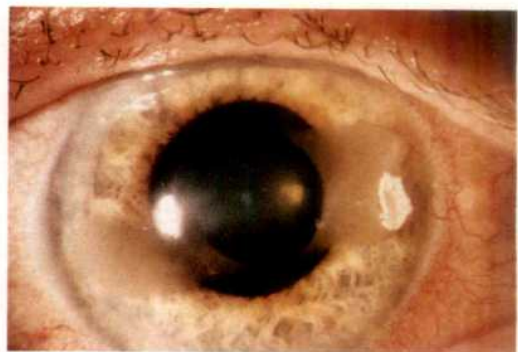


Figure 7B.

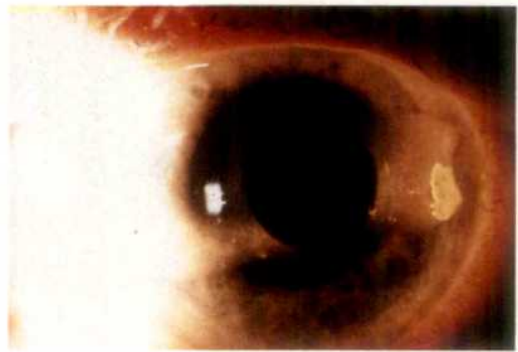


Figure 7C.

Figure 7 Case 4. Even, diffuse band keratopathy. (A) Preoperative appearance showing an even, diffuse band keratopathy – granular in places. (B) The appearance three months after excimer ablation of a single, central 'on-axis' zone to clear the visual axis. The increased clarity of the central ablated zone is evident, and the slight central haze represents lenticular opacity. (C) Postoperative appearance at three months utilising sclerotic scatter to highlight the clarity of the treated area. Note the remarkable clarity of this central zone (underlying lenticular opacities now being excluded).

tube insertion, and revision. He had discomfort and the vision was perception of light with poor projection. There was a dense band keratopathy and a grossly roughened corneal surface with disrupted epithelium (Fig 5A).

In August 1988 he had ELSK. The large central calcium deposit was completely ablated with HPMC to mask the surrounding tissue (Fig 2B). After re-epithelialisation he has remained asymptomatic. Eighteen months later the central corneal zone was still clear and the more peripheral band remnants were unchanged.

GROUP 2. SMOOTH BAND KERATOPATHY

Case 3

A 23-year-old West Indian male had pulmonary

Figure 8 Case 5. Even, diffuse band keratopathy. (A) Preoperative appearance showing an even band keratopathy distributed over the inferior cornea. Deep, white stromal deposits and a dense cataract can also be seen. (B) Postoperative appearance at 48 hours. The overlapping zones of ablation are clearly seen. Re-epithelialisation was complete at this stage. (C) Appearance at one year. Although the ablation zones are still clearly seen, there are signs of calcium deposition along the margins of some of the ablation sites and in the centre of two of these zones. The patient was still asymptomatic.



Figure 8A.

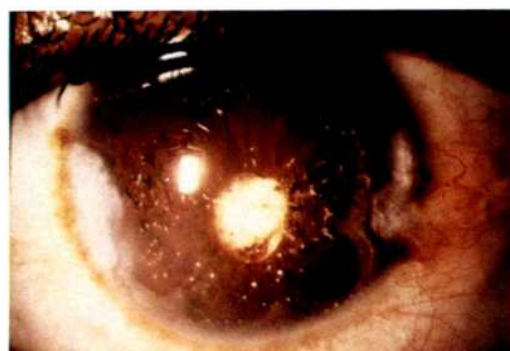


Figure 8B.

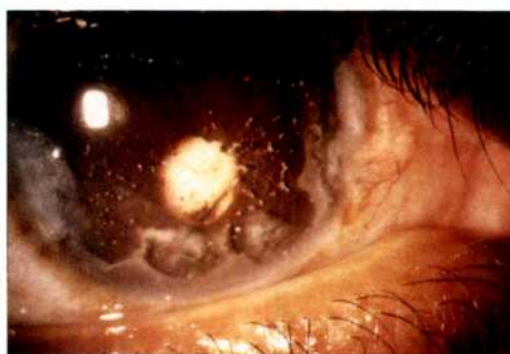


Figure 8C.

sarcoidosis and bilateral panuveitis, the left eye being worse than the right. Acuities were 6/6 right, hand movement left. There was a fine, even band keratopathy across the lower two thirds of the left cornea with early peripheral changes in the right eye.

In June 1988 he had left ELSK with a 3 mm diameter beam centred on the visual axis. Approximately 200 pulses were delivered, of which 150 were required to remove the epithelium. Re-epithelialisation was complete within 48 hours.

One year later the visual acuity had improved to 6/12, though no conclusions can be drawn from this improvement, since the panuveitis had responded to treatment (Fig 6A). The surface quality postoperatively was best demonstrated by photokeratoscopy (Figs 6B, C).

Case 4

A 72-year-old male had bilateral idiopathic evenly distributed band keratopathy (Fig 7A). He had no discomfort but complained of glare and impaired vision: 6/24 right and 6/18 left. He had a right 4 mm axial ELSK without HPMC and the appearance at three months is seen in Figs 7B and 7C. Fig 7C, using sclerotic scatter, highlights the clarity of the central cornea compared to the adjacent band keratopathy against the background of the dilated pupil. Visual acuity in the right eye improved to 6/12, but veiling glare was subjectively unchanged.

Case 5

A 32-year-old Jamaican female had been blind in the right eye (no perception of light) from childhood. The cause was unknown. The eye was very uncomfortable. The left eye was normal.

There was a moderately dense band keratopathy across the inferior two thirds of the right cornea and discrete white deep stromal deposits in the same area (Fig 8A). There was seclusio pupillae and a dense cataract. ELSK was carried out with five 3 mm diameter partially overlapping zones (Fig 8B). Within 48 hours she was asymptomatic with an intact epithelium.

One year after treatment she had occasional mild photophobia. There was a faint anterior stromal haze in areas of ablation, with evidence of recurrence of band keratopathy in the centre of these zones, with a further peripheral deposition causing irregular boundaries (Fig 8C).



Figure 9A.

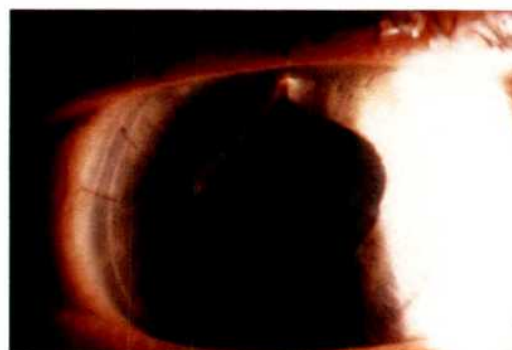


Figure 9B.

Figure 9 Case 6. Dense, even band keratopathy treated with overlapping ablation zones in order to clear the entire corneal surface. (A) Preoperative appearance. A dense, even band keratopathy extends across most of the cornea. Silicone oil was present in the anterior chamber, shown by the reflex which delineates its margin underlying the 10/0 nylon sutures from previous cataract surgery. (B) Appearance three months following excimer laser ablation utilising overlapping and contiguous zones. There has been total clearance of the calcium leaving a smooth, clear cornea. Slight residual haze represents deep, pre-existing, stromal scarring.

Case 6

A 67-year-old male developed a dense evenly distributed band keratopathy in his right eye after retinal detachment surgery which had included injection of silicone oil (Fig 9A). He had also undergone extracapsular cataract extraction with insertion of a posterior chamber intraocular lens. Before photoablation there was only a limited view into the anterior chamber in which silicone oil was present. Vision was hand movements in the inferior field only. ELSK was undertaken for cosmetic reasons and to improve the view of the posterior segment.

Overlapping ablation zones were used to clear the cornea of band. 1% HPMC was used to mask previously ablated areas. At three months the cornea was clear; with an optically smooth surface (Fig 9B). A good view of the anterior chamber, intraocular lens and retina was obtained. As expected, there was no significant improvement in vision.

GENERAL COMMENTS

No patients reported discomfort during the procedure. Postoperatively most of them experienced some discomfort for 24–48 hours. The intensity and duration of discomfort was related to the area of ablation. All patients required oral analgesics for 24 hours. In all cases re-epithelialisation was complete by 48 hours.

Sixteen of the 25 patients had an improvement in visual acuity (Tables 1–5). The 13 patients with uneven, symptomatic (painful) corneal surface became symptom free.

Improvement in visual acuity occurred in those patients who had an even band keratopathy which responded well to photoablation with minimal or no masking. In the seven patients troubled by glare (typically eyes with good visual potential and an evenly distributed 'ground glass' band keratopathy) all were markedly improved postoperatively. Three patients in the series were pleased with the improved appearance of their eyes.

In most of the cases treated it was impossible to assess the central endothelium preoperatively owing to the overlying band keratopathy. Examination by slit-lamp specular microscopy was carried out postoperatively at various stages of the follow-up, and none of the patients was found to have any endothelial disturbance.

Discussion

Our studies have not identified any complications or undesirable findings that would preclude further investigation of the clinical use of excimer lasers in ophthalmic practice.

Excimer laser ablation is a surface phenomenon and therefore irregular surfaces cannot be levelled as a single stage procedure by irradiation. If a rough surface of homogeneous tissue is irradiated, a uniform layer of tissue will be removed with each laser pulse (Fig 10), and in order to produce a smooth surface a masking agent with a similar ablation rate to that of the target material must be used (Fig 11). A liquid more easily ablated than the surrounding tissue would have to be constantly reapplied so as not to

perpetuate surface perturbations. If the ablation rate were less than the surrounding tissue, less frequent applications would be required, and flow of the liquid between laser pulses would ensure that smoothing still occurred.

The viscosity and the surface tension of the masking agent are also of importance. If liquids have high viscosity or surface tension, they may form droplets and, on irradiation, contribute to further surface disturbances rather than smoothing. Surface tension and surface adhesion may also create problems in relation to filling deep surface excavations or those with low aspect ratios in terms of width to depth. The wetting agents selected are in clinical use and have a relatively prolonged contact with the corneal surface. All agents used were adequate for smoothing, but polyvinyl alcohol and 2% HPMC were too viscous and did not have good surface contour-following properties. 1% HPMC, however, was found to have ideal viscosity and was also convenient to apply and remove.

In the laboratory investigations it was possible to produce only models of uneven surfaces with uniform ablation rate – for example, superficial keratectomy beds. While these models are identical to some surfaces encountered clinically, as during lamellar keratoplasty or following removal of pterygia, a special case is encountered

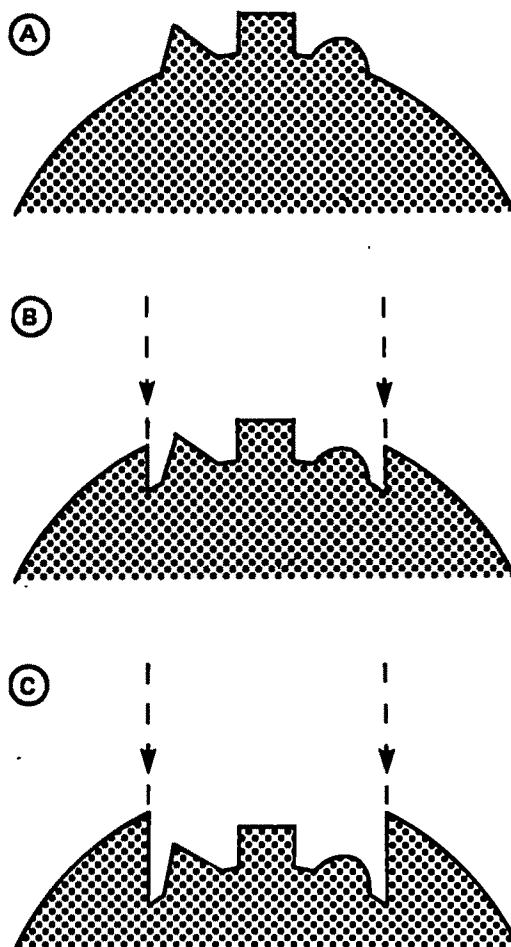
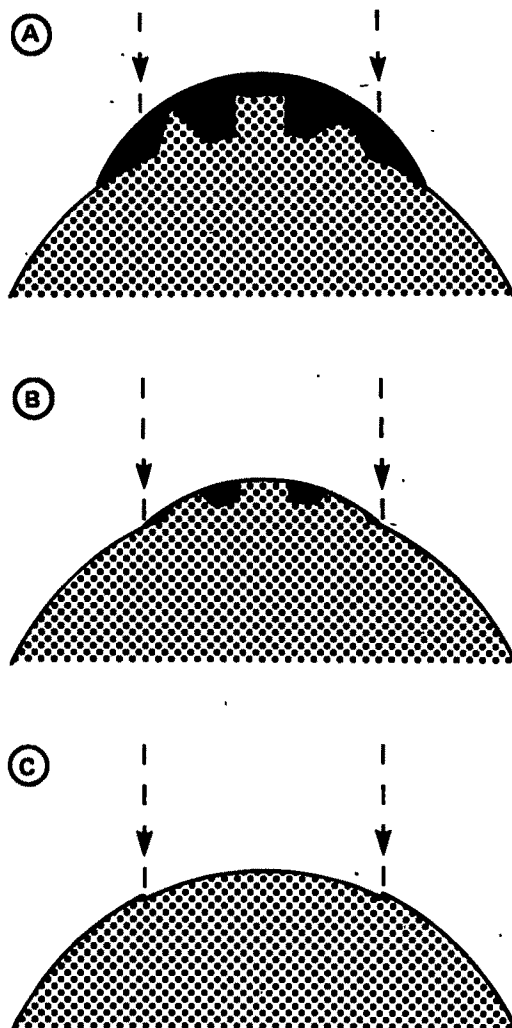


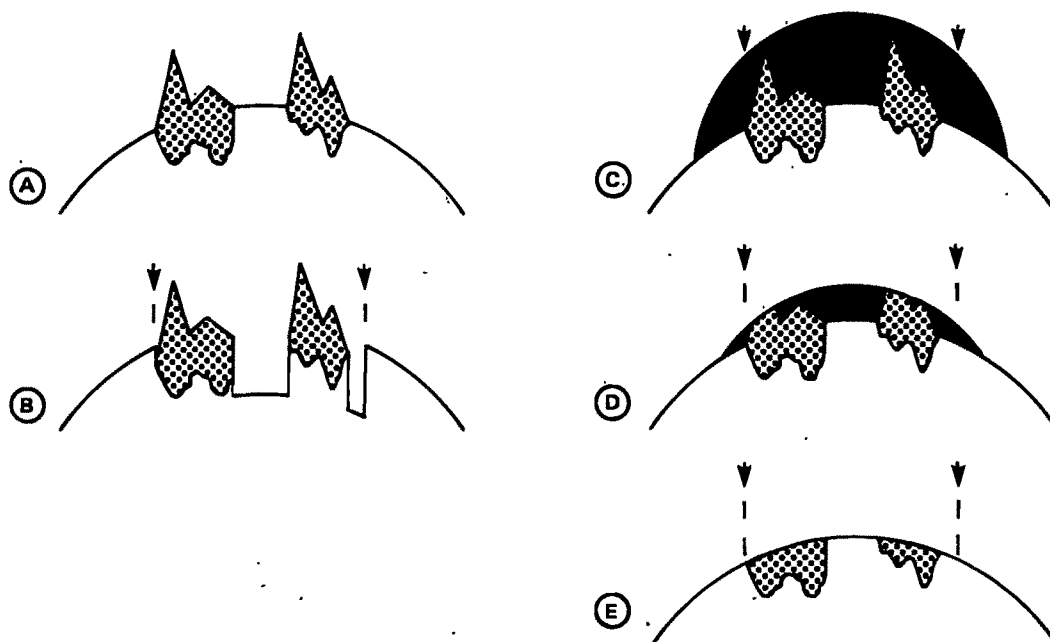
Figure 10 The effect of excimer laser radiation on an unmasked irregular surface. (A) The unexposed surface. (B) After minimal exposure the surface irregularity is repeated deeper into the material, since a uniform layer of equal thickness is ablated across the entire exposed surface with each pulse. (C) The end result is a faithful representation of the original surface topography produced deep in the material.

Figure 11 Production of a smooth surface by excimer laser radiation. (A) The irregular surface, analogous to a rough corneal surface, is covered with a masking liquid. (B) After initial exposure to excimer laser radiation both the masking liquid and surface projections have been partially ablated, the normal stroma between projections having been shielded from unnecessary ablation. (C) The resultant smooth surface at the end of the procedure (determination of the end point is assisted by observation of a uniform fluorescence).



where surface projections are formed by inclusions, such as calcium, with a lower ablation rate than that of intervening tissue troughs (Fig 12). Surface smoothing in this case requires an adjustable 'shield' through which the calcium peaks protrude and are ablated while the troughs are protected. The shield may then be lowered to complete the smoothing process. An ablation

Figure 12 Ablation of dense calcium deposits embedded within the stroma and projecting from the surface. (A) Initial surface. Calcium deposits are shaded. (B) After excimer laser irradiation without masking. The calcium deposits, having a lower ablation rate per pulse, are barely altered from their original heights (dotted line), while the intervening exposed stroma, which has a higher ablation rate, has been unnecessarily excavated (arrows). (C) The same surface shielded with a masking liquid. (D) During ablation only exposed peaks and masking liquid are removed. (E) At the end of the procedure the surface has been smoothed. To remove the remaining calcium deposits embedded in the stroma normal corneal stroma will, of necessity, have to be removed, but its rate of removal can be regulated by further applications of masking liquid.



fluid with a slow ablation rate would be preferable for shielding. In practice, though 1% HPMC may not be optimal, it was certainly adequate as a shielding agent.

The control of the distribution of 1% HPMC during the ablation was an interactive process between manual application and removal. The closed tip size and curvature of Colibri forceps facilitated delivery of small quantities of HPMC without impairing the surgeon's view. Cellulose (Weck-cell) sponges applied to the edge of the target zone were used to remove excess liquid; however, the fluid movement thus created by capillarity was found to be too fast for accurate adjustment. We are now examining alternative sponges whose capillarity engenders less rapid fluid uptake.

All three masking agents fluoresced when irradiated, and the difference in the intensity and wavelength of fluorescence between the masking agent and the corneal substrate was helpful in monitoring the ablation process. The difference in fluorescence was best appreciated when viewing ablation of masked patterns of regular geometry. Discrimination became more difficult during ablation of masked irregular shallow surface perturbations.

It has been shown that the penetration depth of 193 nm radiation is 3–4 μm .⁸ At 248 nm it exceeds 25 μm ; and at 308 nm may be as high as 100 μm .^{25,26} These observations support previous studies using broad band sources of radiation which showed that penetration depth increased with wavelengths between 100 nm and 400 nm.²⁷ Excimer laser radiation at 193 nm does not induce mutagenic response in cells deep to the ablation zone. This has been attributed to two aspects of the ablation process. First, that at the fluences used for clinical procedures the absorption of high energy photons results in bond breaking and ablation, and secondly that virtually no photons penetrate beyond the zone of ablation damaged cells. As a result of target fluorescence longer wavelength photons are generated which have deeper penetration and potential for DNA damage.²⁷ The fluence

associated with such secondary radiation at sites remote from the ablation surface is so low that it has been calculated to be negligible (Sloney D, personal communication). The fluorescence of the masking agent was predominantly in the short wavelength visible portion of the spectrum and was therefore not considered to be a secondary hazard.

The use of masking agents did not affect the nature of the ablated surface, since it was uniform in the pattern experiments (Figs 1B, 2B). Although we did not undertake chemical analysis of the resultant surface after ablation, the homogeneity seen in our morphological studies indicates that no chemical interactions have occurred between the masking liquid and adjacent biological tissues. All surfaces were sealed with a pseudomembrane^{6,8,9,28} as shown by wrinkling (Fig 3B), and previous studies have shown that, whatever the nature of the pseudomembrane, its existence is transitory, and it does not interfere with subsequent healing processes.¹⁴

Although preoperative visual acuity was poor in a large proportion of patients, all except four could fixate with the eye undergoing treatment. In these four patients adequate alignment was achieved with the normal eye fixating an adjustable target at one side of the laser aperture. In only one patient (case 7) was it impossible to treat the band keratopathy because of eye movement.

None of these patients detected the induced fluorescence during ablation in spite of this being clearly visible to all observers. In a further group of patients undergoing photorefractive keratectomy some were aware of a faint blue haze with each pulse. In contrast to the lack of visual stimulation auditory and olfactory sensations were notable. The patients were warned about the noise and the smell of burning, and both were demonstrated prior to the procedure by ablating paper. (The smell is a little disconcerting to some patients as it is rather like that of singed hair.) The biophysics of the smell is difficult to explain. Current concepts of ablation consider that tissue removal occurs owing to a photochemical process of bond breaking rather than a thermal event. Some workers originally considered the process to be an ultrafast thermal event with tissue loss due to massive vibrational modes breaking macromolecular bonds.²⁹ These thermal events could have resulted in 'burn-like' smells. Since the molecular fragmentation depends on wavelength, most workers now consider that ablation is a photochemical process with residual energy used to eject fragments from the surface.³ Smells must be related to airborne particles, and the similarity of smell of excimer ablated and thermally damaged biological tissue implies that similar types of particles are generated by both these processes.

Table 2 Rough band keratopathy treated with single 'on axis' ablation

No.	Sex	Age	Band type	Aetiology	Preop. symptoms	VA	Postop. symptoms	Follow-up		
								VA	Time (months)	Comment
9	F	20	Central Ca ⁺⁺ plaque	Uveitis from childhood	Poor cosmesis	NPL	Improved cosmesis	NPL	10	Epithelial ablation only required
10	F	80	Rough, central Ca ⁺⁺ deposit	Interstitial keratitis	Pain, epiphora	2/60	Marked improvement	2/60	12	Stable

Table 3 Disorders resulting in rough corneal surfaces treated by excimer ablation

No.	Sex	Age	Description	Pathology	Preop. symptoms	VA	Postop. symptoms	Follow-up		
								VA	Time (months)	Comment
11	M	27	Mucus plaque	Atopic, vernal eye disease	Pain, photophobia decreased VA	6/60	Asymptomatic	6/18	14	Re-epithelialised, no plaque recurrence
12	F	45	Rough, raised granular dystrophy	Recurrent granular dystrophy in a PK	Soreness, photophobia decreased VA	6/24	Asymptomatic	6/18	30	No recurrence
13	F	46	Extensive lattice dystrophy	Lattice dystrophy	Glare, photophobia decreased VA	6/60	Asymptomatic Marked increase in VA	6/9	6	No recurrence, no glare, hyperopic shift
14	F	46	Central raised nodules	Salzmann's	Discomfort, decreased VA	6/18	Asymptomatic	6/12	10	Stable
15	F	82	Anterior stromal scarring	Cogan's epithelial dystrophy	Decreased VA, recurrent erosion	4/60	Asymptomatic, improved VA	6/12	10	Stable. Central area treated

PK = punctate keratitis.

Table 4 Smooth surface band keratopathy treated with multiple overlapping ablation zones

No.	Sex	Age	Band type	Aetiology	Preop. symptoms	VA	Postop. symptoms	Follow-up		
								VA	Time (months)	Comment
16	F	32	Even, inferior cornea	Trauma in childhood	Discomfort	NPL	Asymptomatic	NPL	30	Stable, recurrence after 18 months (minimal)
17	M	67	Even, dense thick band	Failed RD surgery; silicon oil in AC	Glare, decreased VA Poor cosmesis	HM	Glare unchanged Good cosmesis	CF	12	Recurrence after 6 months
18	F	81	Even, moderately dense	Idiopathic	Decreased VA, glare	6/18	Reduced glare	6/18	12	Refraction change
19	F	45	Even	Uveitis, glaucoma surgery	Glare and decreased VA	6/9	Glare greatly improved but VA reduced	6/18	12	Refraction change and irregular astigmatism
20	F	70	Even, fine	Idiopathic	Decreased VA. Ablation to improve view for ECCE and IOL	6/36	Improved VA	6/12	10	ECCE/IOL facilitated

AC=anterior chamber. ECCE=extracapsular cataract extraction. IOL=intraocular lens. HM=hand movements.

Table 5 Smooth surface band keratopathy treated with 'on axis' single ablation zone.

No.	Sex	Age	Band type	Aetiology	Preop. symptoms	VA	Postop. symptoms	Follow-up		Comment
								VA	Time (months)	
21	M	23	Even, fine	Uveitis	Decreased VA	6/36	Improved VA	6/9	30	Cornea remains clear, refraction change
22	M	84	Even, fine	Idiopathic	Decreased VA, glare	6/24	Decreased glare Improved VA	6/12	14	Refraction change
23	F	73	Even, fine	Idiopathic	Decreased VA	6/36	Improved VA	6/18	14	Refraction change
24	F	82	Even, fine	Idiopathic	Decreased VA, glare	6/36	Reduced glare Improved VA	6/18	6	Cornea remains clear
25	F	14	Even, fine	Uveitis	Decreased VA, glare	3/60	Glare reduced, slightly improved VA	6/60	12	

Tables 1 to 5 show that postoperative progress was related to the extent of the initial pathology. Systematic analysis of the patient subsets was difficult, because there were significant variations in pathology. However, all patients with rough band keratopathy who had experienced pain preoperatively became asymptomatic (Tables 1 and 2). Most were treated with several overlapping ablation zones in order to smooth the cornea completely (Tables 1 and 2). Table 2 includes those patients who had a relatively small rough central area of band which was successfully treated with a single central ablation. In four patients visual acuity improved. Those with no improvement had extensive pathology of which the band formed only one part.

Four of the five patients with allied disorders which resulted in a rough corneal surface showed an improvement in visual acuity. Those with symptoms of soreness, pain, and photophobia were rendered asymptomatic (Table 3).

Smooth surfaced band deposition was treated with either several overlapping ablation zones (Table 4) or a single 'on-axis' ablation 4 mm in diameter (Table 5). The principal symptoms were reduced visual acuity and glare. Those patients with glare had a marked improvement which was sustained throughout the follow-up period (6 months to 2½ years). In the group treated with overlapping zones one patient showed an increase in visual acuity, one a reduced visual acuity, and the other three no significant difference. Where refraction results could be obtained, a 'plus shift' – that is, towards hypermetropia – was noted (cases 18 and 19, Table 6). In case 19 glare was markedly improved but acuity decreased. This reduction was due to irregular astigmatism because of the faceted surface generated by overlapping ablation zones. In contrast, in the group in which a central 'on-axis' zone was ablated (Table 5) visual acuity was improved in each case and glare reduced. In three of these cases a hyperopic shift was noted. In those patients in whom measurements were possible the mean hyperopic shift was 2.85 dioptres (Table 6).

From this study, which is the first reported series of corneal disease treated with an excimer laser, it is possible to put forward recommendations for selection of patients. First, for patients with rough band keratopathy the excimer laser provides successful treatment. All patients with pain and photophobia became asymptomatic (in general these eyes will have limited visual potential owing to the underlying pathology). Secondly, where the pathology is limited to the

Table 6 Refraction results before and after ablation (where applicable)

No.	Preop. VA	Refraction	Postop. VA	Refraction
18	6/18	+3.00 DS	6/18	+5.50 DS
19	6/9	Plano	6/18	+4.00 DS/-2.50 DCx 85
21	6/36	Plano	6/9	+1.50 DS
22	6/24	+1.00 DS	6/12	+4.50 DS
23	6/36	+0.50 DS	6/18	+5.00 DS/-1.75 DCx 35

anterior stroma pain relief is likely to be accompanied by an improvement in visual acuity. Thirdly, in eyes with good visual potential it is best not to clear all of the band keratopathy by using overlapping ablation zones, since, although glare will be markedly reduced, irregular astigmatism may result, which could lead to reduced visual acuity. Thus a single, axial zone of ablation should be employed. We have also shown that a hyperopic shift occurs when the central cornea is ablated, and patients should be warned about the possibility of anisometropia.

The hyperopic shift (equivalent to a myopic correction) was an unexpected finding as the smoothing procedure is not analogous to photo-refractive keratectomy. This flattening of the cornea implies that some form of differential ablation must have occurred.^{9 15 17 18 30} There are several potential mechanisms that could account for this. First, if the band progressively thinned towards the visual axis, constant irradiance from the laser would effect greater ablation centrally and induce a hyperopic shift. This effect would be enhanced if the ablation rate of the band was less than stroma. In essence, if bands do have such a topography, they act rather like the lens masks currently under investigation for correcting refractive errors. Secondly, although excimer laser radiation will remove an even layer of tissue regardless of the curvature of the surface, the subsurface structure of the cornea is laminated. Removal of central portions of corneal lamellae could lead to centrifugal differential contraction and central flattening. Thirdly, the centrifugal spray of particles of debris and ablation products might be expected to shield the stroma and would theoretically provide progressively greater shielding towards the edge of the ablated zone. Fourthly, the increased obliquity of incident radiation falling on more peripheral cornea might result in a relative decrease in energy density as the edge of the ablation zone is approached. It is unlikely, however, that the degree of differential ablation encountered could arise from inhomogeneities in the excimer beam.

In conclusion, given the encouraging results, the ease with which the procedure can be performed, the patient acceptance of the procedure, and the fact that we have treated all cases on an outpatient basis, we consider excimer ablation the treatment of choice for these cases.

We are indebted to the Iris Fund for continuing financial support in relation to both the purchase of the excimer laser and the provision of a research fellowship for Mr Gartry. We would also thank Summit Technology for their extensive technical help during the course of this work. We are grateful to the consultant staff of St Thomas's Hospital and Mr R J Marsh of the Western Ophthalmic Hospital for referral of patients. Finally, we thank Mrs Ann Patmore for technical support, Sister A Welch, whose help was invaluable in the clinical work, and Mrs J Krafft for her secretarial assistance.

- 1 Trokel SL, Srinivasan R, Braren B. Excimer laser surgery of the cornea. *Am J Ophthalmol* 1983; **96**: 710-5.
- 2 Srinivasan R, Mayne-Banton V. Self-developing photo-etching of polyethylene terephthalate films by far ultraviolet excimer laser radiation. *Appl Phys Lett* 1982; **41**: 576-8.
- 3 Garrison BJ, Srinivasan R. Laser ablation of organic polymers: microscopic models for photochemical and thermal processes. *J Appl Phys* 1985; **57**: 2909-14.
- 4 Rice S, Jain K. Direct high-resolution excimer laser photo-etching. *Applied Physics* 1984; **A33**: 195-8.
- 5 Deutsch TK, Geis MW. Self-developing UV photoresist using excimer laser exposure. *J Appl Phys* 1983; **54**: 7201-4.
- 6 Marshall J, Trokel S, Rothery S, Schubert H. An ultrastructural study of corneal incisions induced by an excimer laser at 193 nm. *Ophthalmology* 1985; **92**: 749-58.
- 7 Puliafito CA, Stienert RF, Deutsch TF, Hillenkamp F, Dehm EJ, Adler CM. Excimer laser ablation of the cornea and lens. Experimental studies. *Ophthalmology* 1985; **92**: 741-8.
- 8 Marshall J, Trokel S, Rothery S, Krueger RR. A comparative study of corneal incisions induced by diamond and steel knives and two ultraviolet radiations from an excimer laser. *Br J Ophthalmol* 1986; **70**: 482-501.
- 9 Marshall J, Trokel S, Rothery S, Krueger RR. Photoablative reprofiling of the cornea using an excimer laser: photorefractive keratectomy. *Lasers in Ophthalmology* 1986; **1**: 21-48.
- 10 Yamaguchi T, Polack FM, Kaufman ME. Endothelial damage after anterior radial keratotomy: an electron microscopic study of rabbit cornea. *Arch Ophthalmol* 1981; **99**: 2151-8.
- 11 Bende T, Seiler T, Schilling A, Wollensak J. Reproduzierbarkeit von Exzisionstiefen bei der Laser-Hornhautchirurgie. In: Wollensak J, ed. *Laser in der Ophthalmologie*. Stuttgart: Enke, 1988: 148-52.
- 12 Seiler T, Bende T, Wollensak J, Trokel S L. Excimer laser keratectomy for correction of astigmatism. *Am J Ophthalmol* 1988; **105**: 117-24.
- 13 Marshall J. Lasers in ophthalmology: The basic principles. *Eye* 1988; **2** (suppl): S98-S112.
- 14 Marshall J, Trokel S, Rothery S, Krueger RR. Long-term healing of the central cornea after photorefractive keratectomy using an excimer laser. *Ophthalmology* 1988; **95**: 1411-21.
- 15 Munnerlyn CR, Koons SJ, Marshall J. Photorefractive keratectomy: a technique for laser refractive surgery. *J Cataract Refract Surg* 1988; **14**: 46-52.
- 16 Tuft S, Marshall J, Rothery S. Stromal remodelling following photorefractive keratectomy. *Lasers in Ophthalmology* 1987; **1**: 177-85.
- 17 Seiler T, Kahle G, Kriegerowski M, Bende T. Myopic excimer laser (193 nm) keratomileusis in sighted and blind human eyes. *Refract Corneal Surg* 1990; **6**: 165-73.
- 18 Macdonald M B, Frantz J M, Klyce SD, et al. One year refractive results of central photorefractive keratectomy for myopia in the non-human primate cornea. *Arch Ophthalmol* 1990; **108**: 40-7.
- 19 Tuft SJ, Boulton ME, Marshall J. Assessment of corneal wound repair in vitro. *Curr Eye Res* 1989; **8**: 713-9.
- 20 Tuft SJ, Zabel R W, Marshall J. Corneal repair following keratectomy: a comparison between conventional surgery and laser photoablation. *Invest Ophthalmol Vis Sci* 1989; **30**: 1769-77.
- 21 Dehm EJ, Puliafito CA, Adler CM, Steinert F. Corneal endothelial injury in rabbits following excimer laser ablation at 193 nm and 248 nm. *Arch Ophthalmol* 1986; **104**: 1364-8.
- 22 Nuss RC, Puliafito CA, Dehm EJ. Unscheduled DNA synthesis following excimer laser ablation of the cornea in vivo. *Invest Ophthalmol Vis Sci* 1987; **28**: 287-95.
- 23 Trentacoste J, Thompson K, Parrish RK, Hajek A, Berman MR, Ganjei P. Mutagenic potential of a 193 nm excimer laser on fibroblasts in tissue culture. *Ophthalmology* 1987; **94**: 125-129.
- 24 Zabel RW, Tuft SJ, Fitzke FW, Marshall J. Corneal topography: a new photokeratoscope. *Eye* 1989; **3**: 198-301.
- 25 Pitts DG, Cullen AP, Hacker PD. Ocular effects of ultraviolet radiation from 295 nm-365 nm. *Invest Ophthalmol Vis Sci* 1977; **16**: 932-9.
- 26 Berlin MS, Martinez M, Papaioannou T, Grundfest W, Goldenberg T, Laudenslager J. Goniophotocoablation: Excimer laser glaucoma filtering surgery. *Lasers Light Ophthalmol* 1988; **2**: 17-24.
- 27 Seiler T, Bende T, Winckler K, Wollensak J. Side effects in excimer corneal surgery. *Graefes Arch Clin Exp Ophthalmol* 1988; **226**: 273-6.
- 28 Kerr Muir MG, Trokel SL, Marshall J, Rothery S. Ultrastructural comparison of conventional surgical and argon fluoride excimer laser keratectomy. *Am J Ophthalmol* 1987; **103**: 448-53.
- 29 Andrew JE, Dyer PE, Forster D, Key PM. Direct etching of polymeric materials using XeCl laser. *Appl Phys Lett* 1983; **43**: 717-9.
- 30 Taylor DM, L'Esperance FA, Del Pero RA. Human excimer laser lamellar keratectomy: a clinical study. *Ophthalmology* 1989; **96**: 654-64.

Glaucoma in Hansen's disease

R C Walton, S F Ball, V C Joffrion

Abstract

Glaucoma is considered to be an uncommon complication of Hansen's disease (leprosy). This study determined the prevalence and characteristics of glaucoma in a large institutionalised leprosy population. All 193 patients currently residing at the Gillis W Long Hansen's Disease Center received a complete ophthalmic examination and review of their records. All had been previously treated with dapsone and/or clofazimine. Based on the strict definition of a recorded intraocular pressure ≥ 22 mm Hg and characteristic optic nerve pathology, 19 patients (10%) were found to have glaucoma. Glaucoma secondary to uveitis was noted in 11 of these patients. These findings suggest that the chronic inflammatory process of Hansen's disease, even when treated, may be followed by secondary glaucoma. We recommend that all patients with Hansen's disease receive regular periodic examinations, including slit-lamp biomicroscopy to detect low-grade iridocyclitis and measurement of intraocular pressure.

Hansen's disease (leprosy) continues to be a leading public health problem in developing countries. Current estimates are that 15 million patients are affected worldwide.¹ Over the past 30 years the number of reported cases in the United States has steadily increased as a result of immigration from regions where it is endemic.¹ In 1988, 184 new cases were reported in the United States, with an average of 250 cases reported each year for the 10 previous years.²

Leprosy is a chronic granulomatous disease which affects the skin, peripheral nerves, and the eye and ocular adnexa. The causative agent, *Mycobacterium leprae*, is an acid-fast bacillus that preferentially grows in tissues cooler than 37°C.³ Because of the long incubation period (five years or greater), the route of transmission remains uncertain, though it is thought that the site of entry is the skin or mucosa of the upper respiratory tract.¹

In accordance with the Madrid classification system the disease exists in three forms: lepromatous, borderline, and tuberculoid.³ Lepromatous leprosy has a higher incidence of intraocular complications, such as uveitis, while tuberculoid leprosy is commonly associated with external ocular problems such as keratitis, lepromas, lid nodules, and lagophthalmos. In the borderline form ocular involvement may include any of the problems seen with the other two forms of the disease.³

Glaucoma is considered an uncommon complication of leprosy, with a reported average prevalence of 3-9%.⁴ It is the result of iris bombe due to pupillary seclusion by posterior synechiae

during episodes of acute iridocyclitis.³ A chronic, low-grade anterior uveitis occurs in 17-41% of Hansen's disease patients, especially those with the lepromatous form of the disease.^{3,5,6} Reports of secondary glaucoma are rare despite the considerable percentage of patients with this type of uveitis. The paucity of secondary disease cases may be the result of atrophy and hyalinisation of the ciliary body leading to a decrease in aqueous production.^{7,8} The purpose of this study was to determine the prevalence and characteristics of glaucoma in a large population of patients with leprosy.

Patients and methods

All 193 patients living at the Gillis W Long Hansen's Disease Center in Carville, Louisiana, were included in the study. The centre is a chronic-care facility; most of the residents have chosen institutional care because of the severe skeletal deformities and/or advanced age. Each patient underwent a complete ophthalmic examination and review of records. Those with a history of glaucoma and all patients with an intraocular pressure (IOP) ≥ 22 mmHg or characteristic optic nerve cupping were re-examined. Characteristic optic nerve findings included a cup-to-disc ratio ≥ 0.5 or a cup-disc ratio difference ≥ 0.2 between the eyes. Visual acuity with appropriate optical correction was measured at 20 feet (6m) by a standard Snellen chart. Slit-lamp examination and gonioscopy were performed. Intraocular pressure was measured with the Goldmann applanation tonometer or the Tono-Pen[†]. With dilated pupils a slit-lamp examination of the lens and a fundus examination, with stereoscopic evaluation of the optic nerve with a +78 dioptre lens, were performed on all patients. Perimetric testing was not available on 10 eyes of 19 patients.

Patients were determined to have glaucoma by the following criteria: (1) IOP ≥ 22 mmHg and red-free slit-lamp examination evidence of nerve fibre layer loss with typical glaucomatous cupping; or (2) visual field defects with typical glaucomatous cupping; or (3) a history of persistent IOP ≥ 35 mmHg on no medications.

Information obtained from each record included the age, sex, race, duration of disease, and type of leprosy (Madrid classification). A history of ocular disease and of ocular operations, visual field abnormalities, and highest recorded intraocular pressure were noted. All current ocular medications were listed. For patients in whom media abnormalities prevented optic nerve visualisation the last recorded cup-to-disc ratio was also noted.

The type of glaucoma was determined by chart review, history, and ocular examination. Patients with less than 180° of peripheral anterior synechiae and a history of multiple episodes of

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Table 1 Glaucoma in Hansen's disease (n=193)

Diagnosis	Number of patients (%)
Primary open angle	3 (1.6)
Open angle secondary to uveitis*	7 (3.6)
Exfoliation	1 (0.5)
Primary angle closure	2 (1.0)
Chronic angle closure secondary to uveitis†	4 (2.1)
Combined mechanism	2 (1.0)

*Patients with <180° of peripheral anterior synechiae secondary to uveitis.
†Patients with peripheral anterior synechiae secondary to uveitis.

anterior uveitis were considered to have open-angle glaucoma secondary to uveitis.

Results

Of the 193 patients 165 (85%) were classified as lepromatous, 20 (10%) as borderline, and 8 (4%) as tuberculoid. All patients had received systemic chemotherapy with dapsone and/or clofazimine. Using the strict definition of a recorded IOP ≥22 mmHg and characteristic glaucomatous optic nerve changes, 19 patients (37 eyes) were found to have glaucoma, a prevalence of 10% (19/193). One patient was monocular following enucleation for postoperative endophthalmitis.

Of the 19 patients with glaucoma 12 (63%) were male and seven (37%) were female. The ages of the patients ranged from 46 to 88 years (mean 67.5 years). Seven (37%) were Caucasian, six (32%) were black, and six (32%) were Hispanic. The mean duration of disease was 42.7 years (range, 7–58 years). Fifteen of the cases were classified as lepromatous, three as borderline, and one as tuberculoid. One patient had diabetes mellitus.

The types of glaucoma in this population are shown in Table 1, while the distribution of the types in the 19 affected patients is displayed in Figure 1. All visual field defects were consistent with the diagnosis of glaucoma (no other aetiology was identified in any of the cases).

A summary of the ophthalmic examinations for the 37 affected eyes is presented in Table 2. In patients with a cataractous lens, no evidence of lens-induced glaucoma was noted. The results of visual acuity measurements are displayed in Figure 2. Of the 16 eyes with visual acuity less than 20/200, 9 had visually significant corneal and/or lenticular opacities. The remaining seven eyes had no significant media opacities; poor

Table 2 Summary of ophthalmic examinations (n=37 eyes)

Finding	Number (%)
Cornea	
Superficial keratitis	12 (32)
Interstitial keratitis	6 (16)
Endothelial pigment	4 (11)
Keratic precipitates	5 (14)
Iris	
Segmental atrophy	12 (32)
Pupillary atrophy	1 (3)
Pupillary transillumination	2 (5)
Gonioscopy	
Angle width ≤ grade 1	12 (32)
Trabecular pigmentation > grade 3	2 (5)
Peripheral anterior synechiae >180°	11 (30)
Lens	
Exfoliation	1 (3)
Glaukomflecken	1 (3)
Posterior synechiae	3 (8)
Cataract	6 (16)
Aphakia/pseudophakia	13 (35)
Intraocular pressure (mmHg)	
Range	17–43
Mean (SD)	23.9 (5.6)
Cup-to-disc ratio*	
≤0.5	12 (32)
0.6–0.7	12 (32)
≥0.8	11 (30)

*Three eyes with media opacities and only description of 'glaucomatous cupping' in records were not included.

vision was probably secondary to glaucomatous optic nerve damage alone.

Discussion

The incidence of Hansen's disease in the United States has shown a steady increase over the past 30 years. The number of cases reported annually has increased from 36 in 1957 to a peak of 361 in 1985.² Most of these cases reflect importation from regions where it is endemic, though a small number are indigenous.¹

Ocular involvement occurs in up to 90% of patients with leprosy.³ In lepromatous patients antigen (or possibly living organisms) may persist in the eye long after completion of standard chemotherapy regimens. These patients may also experience episodes of ocular inflammation without signs of clinical activity in other parts of the body.⁹ Glaucoma has been considered to be an uncommon complication of Hansen's disease despite a considerable number of patients with a chronic low-grade anterior uveitis.

We found a 10% prevalence of glaucoma in this population. This compares with the reported average prevalences of 3.9% in various leprosy populations.⁴ The higher prevalence of glaucoma in our population may be related to the fact that it was biased toward older age and longer duration of disease. Moreover, a larger percentage of patients had the lepromatous form of the disease than other leprosy populations surveyed.¹ However, since inpatient treatment of leprosy is no longer compulsory, it is possible that patients with the most crippling disease (including blindness from glaucoma) preferentially elect institutional care. This may result in an apparent increase in the prevalence of these ocular diseases in this leprosy population. There was a correspondingly high association of other uveitis-induced ocular conditions, some of which needed surgery (cataracts, corneal clouding, angle closure), but these were incidental conditions and not causative of the chronic glaucoma reported. Nevertheless, our results are compar-

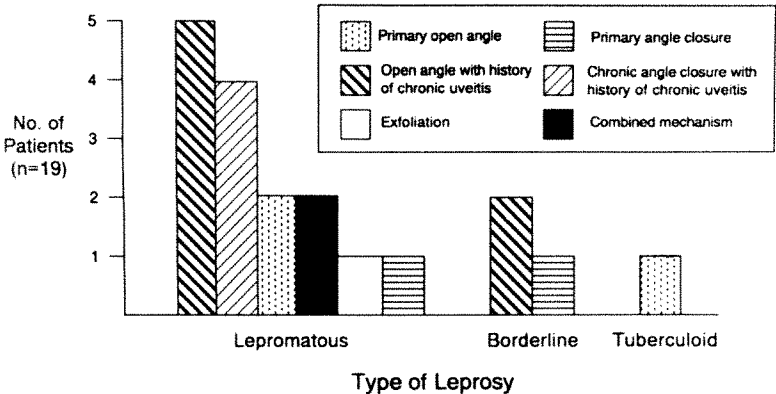


Figure 1 Distribution of types of glaucoma.

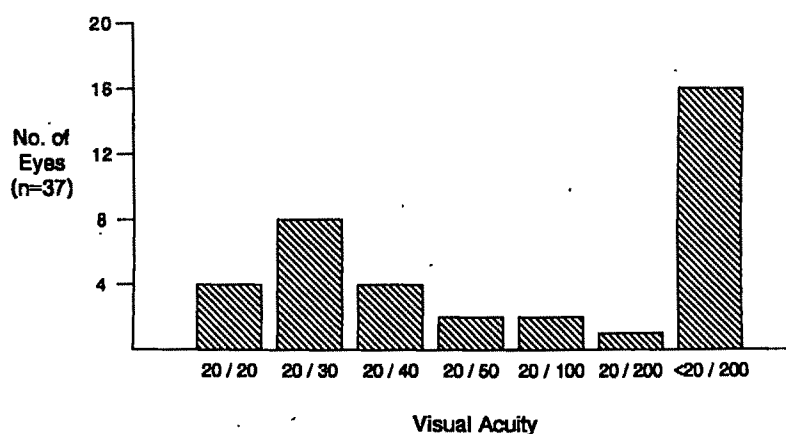


Figure 2 Visual acuity measurements.

able to those of Shields *et al.*,⁵ who found a glaucoma prevalence of 12% in a population with a mean age of 55 years (mean duration of 24 years).

These findings suggest that over time the chronic inflammatory process of Hansen's disease, even when treated, is apt to lead on to secondary glaucoma and severe visual loss. This progression may occur even though the patient has no signs of clinical activity in any other part of the body. Despite these biases we believe that our results should be a useful guide for clinicians treating patients with leprosy – especially those with the lepromatous form, longer duration of

disease, and advanced age. We recommend regular periodic ophthalmic examinations for all patients with Hansen's disease, including those without signs of clinical disease. These examinations should include slit-lamp biomicroscopy to detect low-grade uveitis as well as intraocular pressure measurement. Patients with chronic anterior uveitis should undergo more frequent examination, since they appear to have an increased risk of developing secondary glaucoma.

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- 1 Binford CH, Meyers WM, Walsh GP. Leprosy. *JAMA* 1982; 247: 2283-92.
- 2 Centers for Disease Control. Summary of notifiable diseases, United States, 1989. *MMWR* 1988; 37 (54).
- 3 Schwab IR, Ostler HB, Dawson CR. Ocular leprosy. In: Duane TD, Jaeger EA, eds. *Clinical ophthalmology*. Philadelphia: Lippincott, 1988; 5: chapter 63: 1-8.
- 4 Spaide R, Nattis R, Lipka A, D'Amico R. Ocular findings in leprosy in the United States. *Am J Ophthalmol* 1985; 100: 411-6.
- 5 Shields JA, Waring GO III, Monte LG. Ocular findings in leprosy. *Am J Ophthalmol* 1974; 77: 880-90.
- 6 Malla OK, Brandt F, Anten JG. Ocular findings in leprosy patients in an institution in Nepal (Khotana). *Br J Ophthalmol* 1981; 65: 226-30.
- 7 Siem G. Clinical studies of ocular leprosy. *Am J Ophthalmol* 1971; 71 (suppl): 431-4.
- 8 Brandt F, Malla OK, Anten JG. Influence of untreated chronic plastic iridocyclitis on intraocular pressure in leprosy patients. *Br J Ophthalmol* 1981; 65: 240-2.
- 9 Anonymous. Leprosy and the eye. (Editorial.) *Lancet* 1990; i: 578.

For those patients who should avoid taking nonselective ocular beta blockers...

“Most patients for whom timolol is prescribed are elderly, and disorders likely to be aggravated by beta-adrenergic-receptor blocking agents are common in this age group. **”**¹

When there is a chance of developing cardiopulmonary problems, such as bronchial asthma or heart failure, which may be aggravated by nonselective systemic beta blockade:

...it makes good sense to think selective

Chronic anterior uveitis in leprosy: an insidious cause of blindness

Cesar G Espiritu, Robert Gelber, H Bruce Ostler

Abstract

Chronic low grade anterior uveitis is the commonest cause of blindness in leprosy. It is usually asymptomatic until the late stages, and often patients seek help only after irreversible visual impairment has occurred. We present herewith several cases of this entity to emphasise the insidious nature of the disease, the extent of ocular damage it can cause, and the importance of early detection and treatment.

Leprosy causes ocular damage in four ways: (1) through paralysis of the trigeminal and facial nerve, resulting in lid abnormalities and corneal hypoaesthesia leading to corneal damage, infection, and opacification; (2) through direct bacterial invasion of the external eye, resulting in keratitis, scleritis, and iritis; (3) through iritis, which can occur during the reactional stages of the disease; and (4) through destruction of the autonomic nerve fibres supplying the eye, resulting in pinpoint pupil and a low grade iridocyclitis.

It is estimated that the incidence of iridocyclitis ranges from 5.3% to 63%,¹⁻⁵ depending on the population studied and the completeness of examination.⁶ Acute anterior iridocyclitis is uncommon and occurs bilaterally. It develops during the reactional state erythema nodosum leprosum (ENL), is probably related to reduction of the T-suppressor cells, and is mediated through immune complex deposition.^{7,8} The acute iritis causes symptoms and signs so severe as to make the patient seek medical care.

The commonest form of anterior uveitis in leprosy is a chronic, low grade bilateral uveitis which produces minimal or no symptoms until late in the disease process. Cataracts, synechiae, pinpoint pupils, glaucoma, iris atrophy, and ciliary body damage occur insidiously, resulting in loss of vision. It has been postulated that this form of uveitis is neuroparalytic in origin.^{9,10}

We present here five cases of chronic anterior uveitis in patients with lepromatous leprosy. Our cases emphasise the effects on the eye and the need for early detection, treatment, and frequent monitoring of the eye problem as part of the concurrent treatment of the systemic disease.

Materials and methods

We selected five cases of chronic low grade iridocyclitis after reviewing 25 consecutive records of patients with a diagnosis of iridocyclitis followed at the Hansen's Disease Centre, San Francisco. All cases were multibacillary and represented only part of the clinic's total cases of iridocyclitis. Besides the primary criteria of presenting with a chronic type of anterior uveitis,

other bases for selection included: (1) adequate follow-up and monitoring, with the last visit within three months of the study; and (2) completeness of the medical as well as ocular records.

The ocular examination in each patient had included a visual acuity examination, slit-lamp examination, applanation tonometry, corneal anaesthesiometry, and Schirmer tests.

Results

All five cases illustrate the known characteristics of this commonest form of uveitis in Hansen's Disease. We present one patient in depth and the others in summary form through Table 1.

CASE REPORT

A 72-year-old man with lepromatous leprosy (LL) for eight years was initially treated with dapsone (DDS) 50 mg per day and rifampicin 600 mg per day. Rifampicin was discontinued in 1987 but he continued to take DDS. In 1985 he developed erythema nodosum leprosum and was treated with thalidomide 300 mg per day for eight months. His disease was subsequently relatively quiescent except for the ENL reaction.

In 1985 we saw the patient for routine ocular screening. He had no ocular complaints. Examination revealed no redness, and a visual acuity of 20/30 in both eyes. There were 1+ cells and flare, fine keratic precipitates, and Koeppe nodules without evidence of posterior or anterior synechiae. The intraocular pressures were 13 mmHg in each eye. The patient was treated with dexamethasone 0.1% four times daily and phenylephrine 10% twice daily. Three months later the eyes were quiet, and we reduced the medication to twice daily.

When seen two months later the patient had no symptoms, and his visual acuity had not changed, but he was found to have 1+ cells and flare in the left eye. There were no Koeppe nodules. Bilateral trichiasis and superior superficial keratitis secondary to Hansen's disease were also evident. The intraocular pressures were 8 mmHg in each eye. We increased his dexamethasone to four times daily, phenylephrine to three times daily, and added cyclopentolate 1% twice daily. The patient improved, and after two months the iridocyclitis had cleared, and the dexamethasone and phenylephrine were continued once daily.

Six months later the patient had a complaint of mild redness of the left eye and volunteered that he had used the medications only sporadically. He was found to have a faint ciliary injection, and the anterior chamber of the left eye had 3+ cells and 2+ flare. There were medium white keratic

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Table 1 Profile of five patients with chronic anterior uveitis

ID	Leprosy classif.	Disease duration (yr)	Treatment	Activity	Ocular symptoms	Iris findings	Visual acuity	IOP	Iritis treatment	Response to treatment
51 yr male Filipino	LL	19	DDS	None	None	OU: 1+ cells-flare fine KPs	OU: 20/30	OU: 13	Prednis, neos, cyclo	Good control
30 yr male Filipino	BT	11	DDS, rifampicin, prednis	None since 1985	Mild redness OS	OS: 1+ cells/flare	20/15 20/30	10 4	Neos, decadr	Good control
29 yr male Filipino	BT	7	Thalidomide, DDS, rifampicin	None	Mild redness and blurring OS	OU: 1+ cells/flare	OU: 20/20	10 11	Prednis, mydrac, neos	Good control
73 yr female Laotian	BT	8	DDS, rifampicin, prednis	None since 1983	Blurring OU, redness, photophobia	OU: 1+ cells/flare	20/50 20/70	4 8	Neos, decadr	Good control

LL=lepromatous leprosy. BT=borderline tuberculoid. DDS=dapsone. Prednis=prednisolone acetate 1% (Pred Forte) ophthalmic solution. Neos=phenylephrine hydrochloride 10% (Neo-Synephrine) ophthalmic solution. Cyclo=cyclopentolate hydrochloride 1% (Cyclogyl) ophthalmic solution. Mydrac=tropicamide 1% (Mydracil) ophthalmic solution. Decadr=dexamethasone phosphate. 0.1% (Decadron) phthalic solution. KP=keratic precipitate. ID=identification.

precipitates and posterior synechiae at the 10 o'clock position. The intraocular pressure was 14 mmHg. We prescribed dexamethasone 0.1% every hour, and phenylephrine 10% three times daily. The patient improved, and the medications were tapered to once daily.

During the following three years the patient had six more episodes of low grade iritis in the left eye. In each instance there were no ocular symptoms. The inflammation responded promptly and adequately to increase in the corticosteroid and phenylephrine, but recurred in spite of maintenance therapy. During the three-year period the intraocular pressures varied between 10 to 15 mmHg. Additional posterior synechiae formed, and about 15° of the pupil are now bound down. He has also developed a posterior subcapsular cataract which has reduced his vision to 20/70.

The other four cases are summarised in Table 1.

Discussion

Ocular complications occur more frequently in leprosy than in any other systemic infection. They cause blindness in about 5% of patients.⁸ Blindness occurs in chronic iridocyclitis from development of a band keratopathy, pinpoint pupil, a non-reactive pupil, pigment deposits on the anterior lens capsule, posterior synechiae, secondary complicated cataract, cyclitic membranes, and secondary glaucoma or hypotony.¹¹

In our five cases we encountered only posterior synechiae and complicated cataracts, which is in marked contrast to other reports of cases in which severe ocular changes were observed.

Two factors probably explain the difference in our results. (1) In our patients the diagnosis of Hansen's disease was made early and treatment was started early (none had evidence of systemic activity when we saw them). (2) The iridocyclitis was detected early and treatment started prior to development of sequelae (all patients with lepromatous leprosy in the Hansen's Disease Program, San Francisco, are screened by the clinic nurse with the aid of a slit-lamp, and any questionable cases are referred to the ophthalmologist, which allows for early diagnosis and treatment of patients with a chronic low grade iridocyclitis).

There are differing views on the genesis of chronic anterior uveitis in leprosy. Several investigators believe it is infective in origin, when bacilli present in the iris and ciliary

body.^{5,11,13} Others believe that there is a neuro-paralytic cause. In theory leprosy bacilli lodge in the non-myelinated autonomic nerves of the iris as part of the generalised bacteraemia that occurs in the early stages of lepromatous leprosy. This causes a slow degeneration of the nerves leading to secondary muscle atrophy with release of toxins that brings about a chronic low grade inflammation. Evidence to support this view has been presented in the literature. ffytche⁹ and Garg *et al*¹⁰ have demonstrated the absence of acid fast bacilli in the aqueous and iris in all specimens taken from cases of lepromatous leprosy with chronic low grade uveitis. The low grade non-specific inflammatory changes observed in their studies, as opposed to an active granulomatous process, suggest that this process is not a result of direct bacterial invasion.

Indirect evidence from previous work also supports the involvement of autonomic nerves of the iris. Pharmacologically Swift and Bauschard¹⁴ described the early autonomic denervation hypersensitivity present in lepromatous patients whose pupils abnormally dilated with L-epinephrine. A poor response to anticholinergic drugs such as atropine observed clinically can also be attributed to a derangement in adrenergic nerve fibres. Hussein *et al*¹⁵ alluded to an autonomic (adrenergic) neuropathy of the anterior segment of the eye of patients with lepromatous leprosy by demonstrating significant postural changes in intraocular pressure (greater than 30%).

If the chronicity and low grade nature of the anterior uveitis arises from muscular atrophy secondary to destruction of iris sympathetic nerves, then the relative dependence of these cases on topical steroids and mydriatics commonly employed in their treatment is readily explained. All of our patients required a maintenance regimen to keep their iritis under control, and we observed that discontinuing topical medications resulted in an increase in the anterior chamber reaction. These patients require sustained therapy and monitoring for as long as this degenerative process persists.

RECOMMENDATIONS

The chronicity, insidious nature of this entity, and the importance of early detection and treatment of its activity and complications cannot be overemphasised. Similarly, early detection and eradication of lepromatous leprosy with the help of modern multidrug therapy may reduce the

incidence of iridocyclitis and its seriously damaging effect on the eye.

Co-ordination and co-operation of the medical and paramedical personnel involved with the delivery of health care to leprosy patients must be established. Ideally, early screening for ocular complications, to detect asymptomatic disease, should be done with a slit-lamp by one who is knowledgeable in its use and of the eye findings present in leprosy. Regular, frequent (every one to six months) eye visits are advisable depending on the severity of the uveitis and its response to therapy. Visual acuity testing, intraocular pressure readings, and slit-lamp examination should be done during each follow-up. In addition, supervision of continuing steroid and mydriatic therapy at home is necessary to ensure proper, sustained management.

- 1 Lamba PA, Santoshkumar D, Arthanariswaran R. Ocular leprosy - a new perspective. *Indian J Lepr* 1983; 55: 490-5.

- 2 Spaide RT, Nattis R, Lipka A, D'Amico R. Ocular findings in leprosy in the United States. *Am J Ophthalmol* 1985; 100: 411-6.
- 3 Ticho U, Ben Sira I. Ocular leprosy in Malawi. *Br J Ophthalmol* 1970; 54: 107-12.
- 4 Rohatgi J, Shorey P, Lamba PA, Sehgal VN. Uveal changes in leprosy. *Indian J Lepr* 1986; 58: 208-15.
- 5 Weerakoon L. Ocular leprosy in Ceylon. *Br J Ophthalmol* 1969; 53: 457-65.
- 6 Courtright PD. Defining the magnitude of ocular complications from leprosy: problems of methodology. *Int J Lepr Other Mycobact Dis* 1988; 56: 566-73.
- 7 Mshana RN. Hypothesis: erythema nodosum leprosum is precipitated by an imbalance of T lymphocytes. *Lepr Rev* 1982; 53: 1-7.
- 8 Murray PI, Kerr Muir MG, Rahi AHS. Immunopathogenesis of acute lepromatous uveitis: a case report. *Lepr Rev* 1986; 57: 163-8.
- 9 Hytche TJ. Role of iris changes as a cause of blindness in lepromatous leprosy. *Br J Ophthalmol* 1981; 65: 231-9.
- 10 Garg SP, Kalra VK, Verma N. Aetiopathogenesis of lepromatous iritis. *Indian J Ophthalmol* 1983; 31: 869-71.
- 11 Suryawanshi N. Clinical manifestations of iridocyclitis in leprosy. *Indian J Lepr* 1985; 57: 549-55.
- 12 Choyce DP. Diagnosis and management of ocular leprosy. *Br J Ophthalmol* 1969; 53: 217-23.
- 13 Cameron AN. Leprosy and its ocular manifestations. *Trans Ophthalmol Soc UK* 1961; 81: 637-40.
- 14 Swift TR, Bauschard FB. Pupillary reactions in lepromatous leprosy. *Indian J Lepr* 1972; 40: 142-5.
- 15 Hussein N, Courtright P, Ostler HB, Hetherington J, Gelber RH. Low intraocular pressure and postural changes in intraocular pressure in patients with Hansen's disease. *Am J Ophthalmol* 1989; 108: 80-3.

Presence of a soluble form of acetylcholinesterase in human ocular fluids

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Abstract

Samples of ocular fluid obtained from normal persons at necropsy and during eye surgery have been assayed for the presence of acetylcholinesterase. Measurable levels could be detected in all samples examined, but levels of acetylcholinesterase in vitreous humour were consistently higher than those in aqueous humour, indicating a possible retinal origin. Polyacrylamide gel electrophoresis revealed that the enzyme of ocular fluid had the same mobility as that of acetylcholinesterase from cerebrospinal fluid. It is probable that acetylcholinesterase is secreted from neuronal structures in the retina into the ocular fluid in an analogous manner to the secretion of acetylcholinesterase from brain neurones into cerebrospinal fluid.

Several studies have demonstrated the secretion of acetylcholinesterase (AChE) from neurones within the mammalian central nervous system,¹⁻⁴ which may account for its presence in human cerebrospinal fluid (CSF)⁵ and in amniotic fluid in cases of neural tube defect.⁶ Indeed, animal studies have demonstrated increased levels of AChE in CSF following electrical and drug stimulation of the brain.⁷⁻⁹ The release of AChE has also been demonstrated in the peripheral nervous system, for example from the phrenic nerve-diaphragm preparation,¹⁰ sympathetic ganglia,¹¹ and nerve plexuses of the ileum.¹² The last may explain its presence in human amniotic fluid in cases of fetal exomphalos.¹³

Appreciable levels of AChE are present in ocular tissues such as the amacrine cells of the retina¹⁴ and the nerve plexuses of the iris.¹⁵ Hence any secretion of AChE from such tissues would be expected to result in detectable levels of enzymatic activity in the fluids of the eye by analogy with the situation in CSF. Although there are some reports from the 1940s of cholinesterase activity in ocular fluids of various mammalian species,¹⁶ no attempt was made to distinguish between AChE and butyrylcholinesterase (BuChE) activities. Furthermore no attempts have been made to confirm these reports by spectrophotometric assay methods.

In an attempt to demonstrate the possible secretion of AChE from neuronal structures within the human eye we have therefore examined human ocular fluids for the presence of AChE and BuChE activities. We have also compared, by polyacrylamide gel electrophoresis, the enzyme forms present with that present in human CSF, which is thought to derive, by secretion, from neuronal structures of the central nervous system.

Materials and methods

COLLECTION OF OCULAR FLUIDS

At necropsy

Ocular fluids were collected at necropsy from persons dying of non-neurological conditions and in whom a past history of eye disease was absent. The eyelids were retracted by hand, and aqueous humour was collected from the anterior chamber by direct puncture through the cornea with a 25 G needle attached to a sterile 1 ml syringe followed by gentle aspiration of the contents. Similarly the vitreous humour was collected from the vitreous cavity by direct puncture through the sclera, posterior to the ciliary body (through pars plana), with a 27 G needle attached to a sterile 2 ml syringe. Any samples in which there was discolouration of the fluid suggesting possible contamination by either iris or retina were discarded. The normal cosmetic appearance of the eye was reconstituted by injecting a similar volume of saline back into the eye chambers.

The ocular fluids were transferred from the syringe to 1.5 ml microfuge tubes and centrifuged for 10 minutes at 12 000 g to sediment particulate matter. The supernatant was then gently aspirated off into another microfuge tube, labelled, snap frozen in liquid nitrogen, and stored at -70°C.

Initially, in order to provide adequate volumes for repeated assays, the vitreous and aqueous humours from one patient were pooled (to give a ratio vitreous:aqueous of 10:1). In later experiments the two types of humour were handled separately.

During eye surgery

Aqueous humours were collected during eye surgery (for cataract removal) from patients with no history of other eye diseases or neurological disease. The skin of the eyelids was prepared for surgery with iodine solution, then dried. The lids were then held open with a speculum and an initial corneal groove made with a diamond knife. A 27 G sterile needle was passed into the anterior chamber via the corneal groove and approximately 0.1-0.15 ml of aqueous humour removed into a 1 ml syringe. This was transferred straight into a sterile microfuge tube and frozen at -20°C within 1 hour.

In six of the patients the surgical procedures were carried out under local anaesthesia (xylocaine), and samples were taken within 10 minutes of retrobulbar injection. The remainder received a general anaesthetic, samples being taken 10-15 minutes after induction of anaesthesia. All patients received premedication

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consisting of phenylephrine and cyclopentolate eyedrops.

COLLECTION OF CEREBROSPINAL FLUID AT NECROPSY

After opening of the cranial cavity, CSF was aspirated from the level of the basal cistern with the exposed brain still in situ. The CSF samples were then centrifuged at 3000 g for 30 minutes at 4°C, and the supernatant was divided into aliquots, snap frozen, and stored at -70°C for up to one year.

BIOCHEMICAL ANALYSIS

Cholinesterase activities were measured by a microversion of the method of Ellman *et al.*,¹⁷ with microtitre plates. Acetylthiocholine was used as substrate at a concentration of 1.0 mM, which is optimal for AChE, but suboptimal for BuChE. The assay was performed at 25°C in 0.05 M Na/K phosphate buffer, pH 7.0 containing 3 mM 5,5'-dithio-bis-(2 nitrobenzoate), in a total volume of 100 µl. The rate of hydrolysis of acetylthiocholine was monitored by measurement of absorbances at 410 nm with a Titertek multiscan microplate reader. A calibration curve was constructed with purified electric eel AChE (Sigma) that had previously been assayed by a stopped assay version of the conventional Ellman assay¹⁸ such that 1 mU cholinesterase activity corresponded to 1 nmol acetylthiocholine hydrolysed per minute at 30°C, pH 7.0. The assay was linear up to an absorbance reading of 2.0. AChE and BuChE activities were distinguished by means of the specific AChE inhibitor BW 284c51 (1.5 µM). All assays were performed in triplicate, with good agreement between them.

Estimation of the protein content of the ocular fluids was performed by a micro version of the Biorad dye-binding assay.¹⁹

Samples of ocular fluids and CSF were analysed by polyacrylamide gel electrophoresis. The gels were incubated with acetylthiocholine to reveal bands of cholinesterase activity,²⁰ with BW 284c51 to distinguish between AChE and BuChE.

STATISTICS

All values are reported as mean with SEM. Differences between activities of aqueous, vitreous, and mixed ocular fluids were tested for statistical significance by Wilcoxon's signed rank test, or the Mann-Whitney U test, as appropriate. Correlations between the activities of AChE and the age of the patient at death, or the post-mortem delay, were analysed by the Spearman rank correlation test. In all cases a value of $p < 0.05$ was taken to indicate statistical significance.

Results

Cholinesterase activity was detectable in all samples of ocular fluid examined, with acetylthiocholine as substrate. Most of this activity was inhibited by the specific AChE inhibitor BW

Table 1 Cholinesterase activities (SEM in parentheses) of different types of human ocular fluid obtained either post mortem or at eye surgery

Ocular fluid	Total ChE activity	AChE activity	% AChE
PM pooled fluids (n=18)	31.4 (3.8)	23.9 (3.3)	75.4 (2.9)
PM vitreous humour (n=5)	20.6 (2.0)	14.7 (1.5) NS	70.7 (1.9)
PM aqueous humour (n=5)	22.6 (1.2)	11.4 (1.2) NS	51.3 (5.2)
Surgical aqueous humour (n=8)	3.9 (0.3)	2.6 (0.5)*	79.4 (7.2)

PM = post mortem. Acetylcholinesterase activities are given in mU per ml CSF. *Significantly different from level in mixed ocular fluids obtained at necropsy (Mann-Whitney U test, $p < 0.001$).

284c51, indicating that the majority of cholinesterase activity was attributable to AChE, while levels of non-specific cholinesterase activity were comparatively low. The AChE activities of total ocular fluid obtained at necropsy were much higher than those detected in aqueous humour obtained during surgery from living patients (Table 1). When aqueous and vitreous humours were obtained separately at necropsy, the AChE activity of the vitreous humour was significantly higher ($p < 0.05$ by Wilcoxon signed rank test)

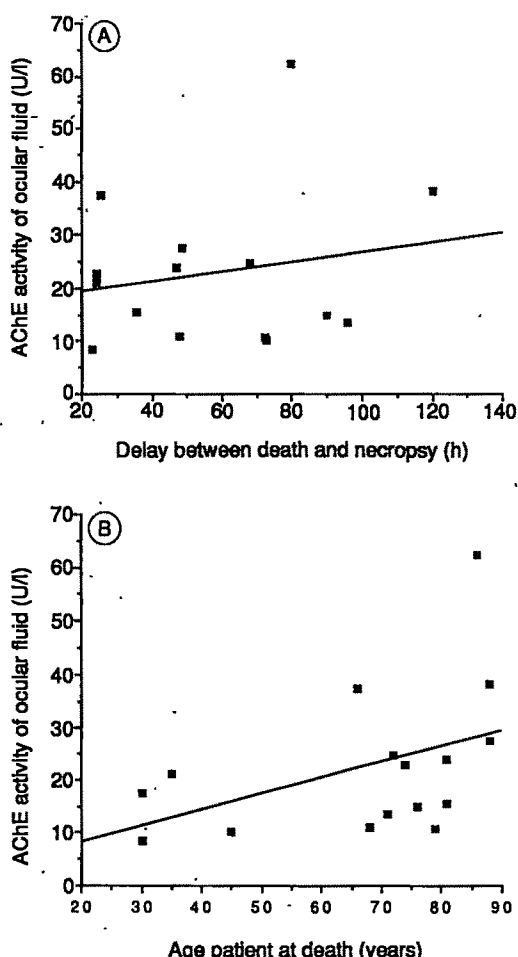


Figure 1 Graphs to show the relationship between AChE activity of ocular fluid obtained at necropsy and (A) the delay between death and necropsy, (B) the age of the patient at death. In each case the line shown is the line of best fit as determined by linear regression using the method of least squares. Spearman rank correlation coefficients indicated that there was no significant correlation between AChE activity and post-mortem delay, but AChE activity was significantly correlated with age.

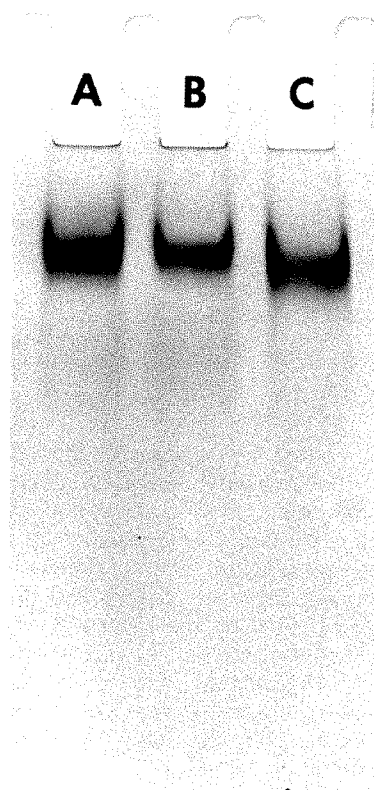


Figure 2 Polyacrylamide gel of ocular fluid and cerebrospinal fluid stained to reveal cholinesterase activity. The samples were applied at the top and the direction of migration was towards the anode. Track A contained ocular fluid obtained at necropsy; track B contained cisternal cerebrospinal fluid obtained at necropsy from the same patient; track C contained a mixture of ocular fluid and cerebrospinal fluid. A similar gel stained in the presence of BW 284c51 had no detectable staining.

than that of aqueous humour from the same eye (Table 1).

There was no significant correlation between AChE activity of the total ocular fluid obtained at necropsy and the delay between death and necropsy, the Spearman rank correlation coefficient being 0.181 ($n=17$) (Fig 1A). However, there was a significant correlation ($p<0.01$) between AChE activity of total ocular fluid and the age of the patient at death, with a Spearman rank correlation coefficient of 0.542 ($n=16$) (Fig 1B).

Polyacrylamide gel electrophoresis of total ocular fluid revealed one band of AChE activity with a similar mobility to that of AChE in CSF obtained from the cisterna magna of the same patient. Indeed, only one band of AChE activity could be detected in a mixture of ocular fluid and CSF (Fig 2).

Comparison of the cholinesterase activities of total ocular fluid and cisternal CSF obtained at necropsy indicates that ocular fluid contains slightly higher levels of AChE activity, but considerably lower levels of BuChE activity, than cisternal CSF (Table 2). The specific activity of AChE in ocular fluid was markedly higher than that of cisternal CSF owing to the much lower levels of protein present (Table 2).

Discussion

These results show that AChE is present in human ocular fluids in appreciable levels while

Table 2 Comparison of cholinesterase activities (SEM in parentheses) of ocular fluid and cisternal CSF obtained post mortem from the same patients

Enzyme	Total ocular fluid	Cisternal CSF
AChE	23.9 (3.3)	21.0 (4.2)
BuChE	13.8 (2.2)	36.4 (13.9)
Protein	0.84 (0.16)	3.7 (0.8)
Specific activity AChE	37.5 (5.9)	3.7 (0.9)

Cholinesterase activities are given in mU and protein contents are given in mg per ml (=g/l) CSF. Specific activities AChE are given as mU AChE activity per mg protein.

levels of BuChE are very low. The levels of AChE detectable in total ocular fluids obtained at necropsy are comparable to those found in CSF also obtained at necropsy from the same patient, though they are slightly higher.

The levels of AChE detectable in total ocular fluids obtained at necropsy are markedly higher than those present in aqueous humour obtained from living patients during eye surgery. This could be explained if the majority of AChE activity observed in total ocular fluid at necropsy derived from the vitreous humour rather than the aqueous humour. The lower levels of AChE activity observed in the aqueous humour compared with the levels in vitreous humour in the few patients from whom the two fluids were collected separately would appear to support this explanation. The results of previous studies in the 1940s also suggest that most of the cholinesterase activity in ocular fluids is confined to the vitreous humours.¹⁶ This is not surprising, since it is the vitreous humour and not the aqueous humour which is in contact with the retina, where the majority of AChE-containing cells of the eye are situated. It is likely that some equilibration of the two pools of fluid would have occurred during the time between death and necropsy thus accounting for the higher levels of AChE found in aqueous humour obtained at necropsy compared with the levels found in living patients.

An alternative explanation for higher levels of AChE observed at necropsy is that they are a post-mortem artefact due to the non-specific release of AChE from the tissues of the eye during the period between death and collection at necropsy. However, if this were the case, the level of AChE activity present in the fluid samples should correlate with the time delay between death and necropsy. As these two parameters were not correlated this explanation is unlikely.

The drug regimens of the patients could also contribute to these differences in AChE activity, since various drugs have been shown to affect the secretion of AChE from the central nervous system into CSF.⁸ Certainly all the surgical patients received the muscarinic antagonist cyclopentolate topically during premedication, and such drugs have been shown to decrease the secretion of AChE into CSF⁹ and from the hippocampus.² It is therefore possible that this drug also decreases secretion of AChE from cholinergic tissues of the eye such as lens, ciliary body, and iris, and therefore causes lower levels of AChE in the aqueous humour.

The AChE activity of total ocular fluid obtained at necropsy was found to increase with

the age of the patient, such that the two were significantly correlated. Previous studies have found a similar effect of age on the AChE activity of CSF.^{21,22}

Polyacrylamide gel electrophoresis indicates that the AChE present in ocular fluid has a similar mobility to that of human CSF; indeed the two activities comigrate in a mixture of the two fluids. The form of AChE present in ocular fluids is therefore likely to be the same as that in CSF. Since the AChE activity in CSF is believed to result from secretion of AChE from the surrounding neuronal tissues, it is also likely that the AChE found in ocular fluids is a result of secretion from the AChE-containing tissues of the eye. It would certainly be worthwhile to investigate, by direct methods, whether basal and evoked secretion of AChE from retinal tissues does occur under normal physiological conditions.

In vitro studies have previously failed to demonstrate any secretion of AChE from the iris,³ which contains appreciable amounts of AChE in nerve plexuses. The results of the present study suggest that secretion of AChE from the tissues of the iris is negligible, at least in humans, since aqueous humour which is in close contact with the iris contains little AChE activity when collected during life (though this could be an effect of cyclopentolate administration).

The functional significance of any secretion of AChE from retinal cells is at present unclear. However, several studies now suggest that secreted AChE may have modulatory effects on the excitability of neurones in the central nervous system.^{23,24} It is possible that AChE could have a similar role in the retina.

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- 1 Greenfield SA, Cheramy A, Levie V, *et al.* In vivo release of acetylcholinesterase in cat substantia nigra and caudate nucleus. *Nature* 1980; **284**: 355-7.
- 2 Appleyard ME, Smith AD. Spontaneous and carbachol-evoked in vivo secretion of acetylcholinesterase from the

- hippocampus of the rat. *Neurochem Int* 1987; **11**: 397-406.
- 3 De Sarno P, Giacobini E, Downen M. Release of acetylcholinesterase from the caudate nucleus of the rat. *J Neurosci Res* 1987; **18**: 578-90.
- 4 Appleyard ME, Vercher JL, Greenfield SA. Release of acetylcholinesterase from the guinea-pig cerebellum in vivo. *Neuroscience* 1988; **25**: 133-8.
- 5 Tower DB, McEachern D. Acetylcholine and neuronal activity: II. Acetylcholine and cholinesterase activity in the cerebrospinal fluid of patients with epilepsy. *Can J Res E* 1949; **27**: 120-31.
- 6 Smith AD, Wald NJ, Cuckle HS, Stirratt GM, Bobrow M, Langerkrantz H. Amniotic fluid acetylcholinesterase as a possible diagnostic test for neural tube defects in early pregnancy. *Lancet* 1979; **i**: 685-8.
- 7 Bareggi SR, Giacobini E. Acetylcholinesterase activity in ventricular and cisternal CSF of dogs. *J Neurosci Res* 1978; **3**: 335-9.
- 8 Greenfield SA, Chubb IW, Smith AD. The effect of chlorpromazine on the concentration of acetylcholinesterase activity in the cerebrospinal fluid of rabbits. *Neuropharmacology* 1979; **18**: 127-32.
- 9 Vogt M, Smith AD, Fuenmayor LD. Factors influencing the cholinesterases of cerebrospinal fluid in the anaesthetised cat. *Neuroscience* 1984; **12**: 797-995.
- 10 Skau KA, Brimijon S. Release of acetylcholinesterase from rat hemidiaphragm preparations stimulated through the phrenic nerve. *Nature* 1978; **275**: 224-6.
- 11 Gisiger V, Vigny M. A specific form of acetylcholinesterase is secreted by rat sympathetic ganglia. *FEBS Lett* 1977; **84**: 253-6.
- 12 Appleyard ME, Smith AD. Secretion of acetylcholinesterase and butyrylcholinesterase from the guinea-pig isolated ileum. *Br J Pharmacol* 1989; **97**: 490-8.
- 13 Wald NJ, Cuckle HS, Barlow RD, *et al.* Early antenatal diagnosis of exomphalos. *Lancet* 1980; **i**: 1368-9.
- 14 Hutchins JB, Hollyfield JG. Acetylcholinesterase in the human retina. *Brain Res* 1987; **400**: 300-11.
- 15 Mattio TG, Richardson JS, Giacobini E. Effects of DFP on iridic metabolism and release of acetylcholine and on pupillary function in the rat. *Neuropharmacology* 1984; **23**: 1207-14.
- 16 De Roeth A. Cholinesterase activity in ocular tissues and fluids. *Arch Ophthalmol* 1950; **43**: 1004-25.
- 17 Ellman GL, Courtney DK, Andres V, Featherstone RM. A new and rapid colorimetric determination of acetylcholinesterase activity. *Biochem Pharmacol* 1961; **7**: 88-95.
- 18 Chubb IW, Smith AD. Release of acetylcholinesterase into the perfusate from the ox adrenal gland. *Proc R Soc B* 1975; **191**: 263-9.
- 19 Bradford MM. A rapid and sensitive method for the quantification of microgram quantities of protein utilising the principle of protein-dye binding. *Anal Biochem* 1976; **72**: 248-54.
- 20 Chubb IW, Smith AD. Isoenzymes of soluble and membrane-bound acetylcholinesterase in bovine splanchnic nerve and adrenal medulla. *Proc R Soc B* 1975; **191**: 245-61.
- 21 Tune L, Gucker S, Folstein M, Oshida L, Coyle JT. Cerebrospinal fluid acetylcholinesterase activity in senile dementia of the Alzheimer type. *Ann Neurol* 1985; **17**: 46-8.
- 22 Appleyard ME, Smith AD, Berman P, *et al.* Cholinesterase activities in cerebrospinal fluid of patients with senile dementia of the Alzheimer type. *Brain* 1987; **110**: 1309-22.
- 23 Greenfield SA, Jack JJB, Last ATJ, French M. An electrophysiological action of acetylcholinesterase independent of its catalytic site. *Exp Brain Res* 1988; **70**: 441-4.
- 24 Appleyard ME, Jahnson H. Non-cholinergic effects of acetylcholinesterase upon the membrane properties of mammalian cerebellar Purkinje cells. *Eur J Neurosci* 1989; suppl 2: 129.

Visual assessment of infants: vernier targets for the Catford drum

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Abstract

Targets comprising a horizontal black line 5' thick offset by 1' were printed on strips to stick to the drums of the Catford Visual Acuity Apparatus. The 'vernier' targets so produced corresponded to the different sizes of Snellen letters from 6/6 to 2/60 when presented at 50 cm. Twenty-five children between the ages of 3 and 12 years with known amblyopia (mostly strabismic) were tested in a double blind trial to compare the visibility of the vernier targets with subjective Snellen acuity. All vernier results, both for better and amblyopic eye, were within one line of Snellen acuity. One hundred and twenty normal preverbal infants with normal eyes under the age of 2½ years were tested with the vernier strips. Normal infants under the age of 6 months recorded a vision of 6/60-2/60; normal infants aged 6 to 12 months recorded 6/24-6/36, and infants between the ages of 1 and 2½ years recorded 6/12-6/18.

Catford and Oliver¹ described an instrument for the objective determination of visual acuity. It consisted of a motor driven drum which could display black dots of various sizes in oscillatory motion against a white background. Acuties were determined by finding the smallest dot which could be fixed and followed by the patient. The drum dot targets were criticised because they subtended five' of arc and were contrast targets, testing merely visibility, thereby giving a marked overestimate of acuity.² The drum method was also criticised because it used a moving target which was presumed to have a synergistic effect by simultaneously exciting a new area of retina while leaving an inhibitory area.³

The forced-choice preferential looking (FPL) method is also used as a means of estimating acuity and other visual detection performance in infants.^{4,5} However, there is often a poor relationship between Snellen letter acuity and

measures of resolution such as grating acuity.^{9,10} Teller acuity cards do not reliably detect strabismic amblyopia.¹¹ The method can be time consuming, variable in older infants, and difficult to interpret in the clinical situation.

Shimojo *et al*¹² described a motor sound display to measure vernier acuity. In this display a pair of striped patterns was presented, one of which contained horizontal vernier offsets on its edges. The displacement of the vernier offsets gave the impression of intermittent motion of a target which was defined by these offsets. The motion was perceived only when the vernier offsets were detected. Vernier acuity, defined as the inverse of the smallest detectable misalignment of edges, gives a resolving power of the order of 4" of arc for the contour break and 0.5" of arc for the line.¹³ It has therefore been termed a type of hyperacuity,¹⁴ which may be considered an outcome of central visual processing.

Atkinson *et al*² stated that in principle they believe the use of an ocular following response to repetitive movement of a discrete target as proposed by Catford and Oliver is a robust method. It offers one of the best chances of rapid and reliable acuity assessment in children aged between 6 months and 2½ years if a better target could be found. Since vernier acuity is known to be less than grating acuity in neonates¹² and in strabismic amblyopes,¹⁵⁻¹⁷ we developed targets with vernier offsets for attachment to the Catford machine so that we might compare the visibility of them with subjective Snellen acuity for a group of amblyopic children whose acuties could be reliably subjectively tested. We also recorded the vernier vision of 120 normal preverbal infants with the same vernier targets.

Apparatus

A black horizontal line on a white background moving horizontally is not perceived to move if the ends of the line are concealed. If the line has a vernier offset and the offset is perceived, the eye may fix and follow it. If targets of decreasing

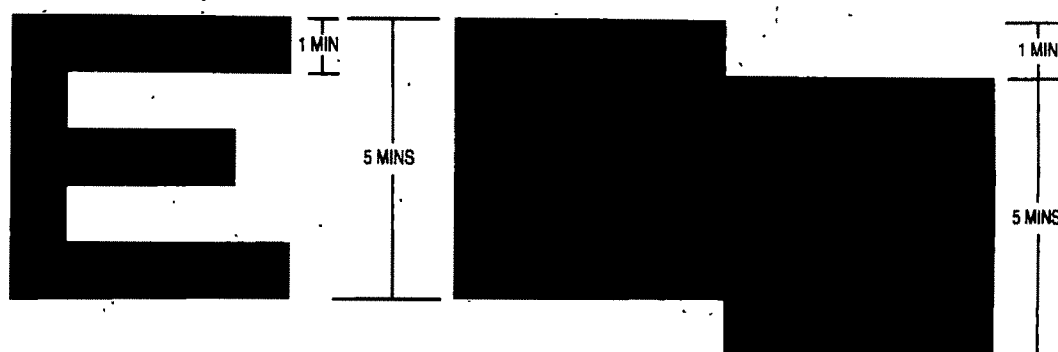


Figure 1 Snellen and vernier targets.

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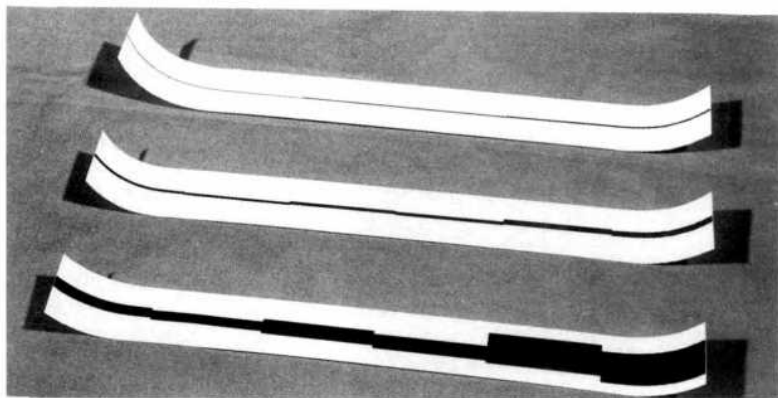


Figure 2 'Vernier' strips.

size are presented, they may be fixed and followed until they are too small to be seen. The smallest target fixed and followed is a measure of some form of vision.

We therefore printed on card strips a line with a vernier offset corresponding to the different sizes of the Snellen letters from 6/6 to 2/60 for presentation at 50 cm. To correspond with Snellen letters the horizontal black line was 5' thick offset by 1' (Fig 1). The ends of the target lines are concealed by the vertical sides of the viewing aperture in the Catford apparatus screen if only three targets are printed on each strip, the full range of 6/60 to 2/60 requiring therefore three strips:

Strip 1 6/6 6/9 6/12.

Strip 2 6/18 6/24 6/36.

Strip 3 6/60 4/60 2/60 (Fig 2).

The strips were stuck to Catford drums. Plain white card strips were stuck to the apparatus screen to narrow vertically the viewing aperture, so that only the line and offset were visible to the subject, and the moving edges of the drum were concealed even if the screen was inadvertently tilted in a vertical direction (Fig 3).

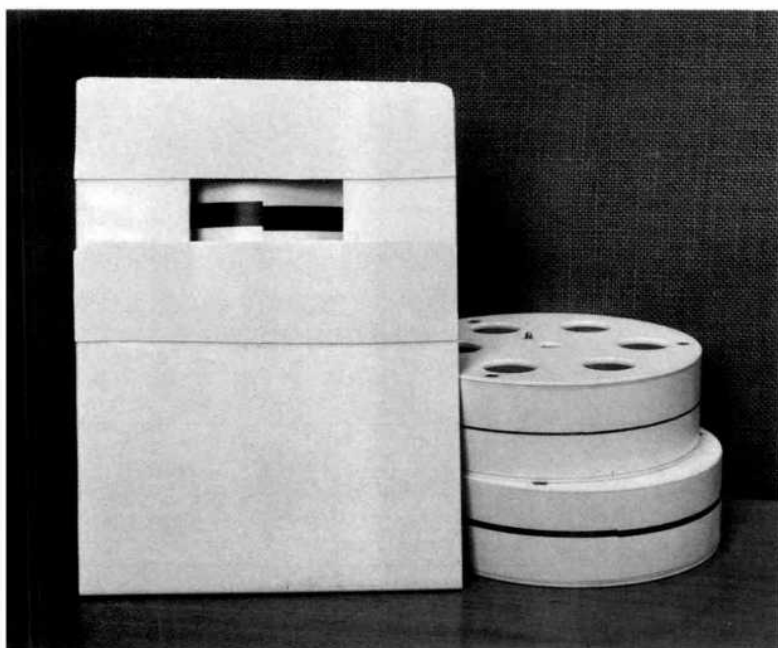


Figure 3 Catford apparatus with 'vernier' strips attached.

Subjects, method, and results

Twenty-five children between the ages of 3 and 12 years with known amblyopia were selected from routine orthoptic clinics by one orthoptist. Another orthoptist, holding the apparatus 50 cm from the subject's eye (the motor operating at speed setting 2) recorded as the vernier acuity the smallest target fixed and followed, starting with the larger targets and presenting smaller and smaller targets until no following movements were observed. Only the smooth pursuit movement of following the offset was recorded; the rapid saccadic movements observed when the offset is temporarily lost to perception and the subject searches for it again were ignored. In the same room under the same lighting conditions, a third orthoptist recorded the Snellen acuity at 6 m. Neither of the recording orthoptists had knowledge of previous acuities nor of the other orthoptist's results.

All vernier results were within one line of Snellen acuity; not one amblyope was missed, and no hyperacuity values were recorded. Most of the children tested had strabismic amblyopia, but one had anisometropia, one a microtropia, one unilateral aphakia and one congenital nystagmus in addition to strabismic amblyopia (Table 1). Further statistical analysis of these results is difficult. One cannot statistically analyse all 50 eyes because of the lack of independence of the data from amblyopic and fellow eye.¹⁸

We recorded vernier visions on 120 preverbal infants under the age of 2½ years who attended our routine orthoptic clinics. These infants, after the test, were all found to be normal optically, orthoptically, and ophthalmologically.

It can be seen that babies in the early months of life have a vernier vision between 2/60 and 6/60. This vision rapidly improves to 6/36–6/24 by 6 months of age and then levels out around 6/18–6/12 after 1 year (Fig 4).

Discussion

The assessment of visual acuity in all children under the age of 2½ years in the clinical situation has always been a problem. In the young, from whom subjective answers are unobtainable, objective measures must be used. Visibility has been measured by Catford dots and Stycar balls; resolution has been measured by preferential looking gratings and checkerboard visual evoked responses, while vernier acuity has been measured in motor display systems in laboratories. None of these methods has proved ideal and comprehensive in the clinical situation. It is extremely difficult, perhaps impossible, to assess recognition clinically in preverbal infants. A small child has a very short span of attention and rapidly becomes bored. When assessing a young child by behavioural methods it is dangerous to assume that a lack of behavioural response to a target means that the target is not perceived or resolved. Any indirect behavioural method of assessment poses the same problem of interpreting a negative result.

One of the main causes of reduced vision in infants and children is amblyopia. It is not yet clear precisely what is the visual difficulty in

Table 1 Comparison of acuities. Vernier strip and Snellen in 25 amblyopic children

Subject	Age (years)	Diagnosis	Better eye		Amblyopic eye	
			Snellen	Vernier	Snellen	Vernier
1	11	LDS	6/6	6/6	6/18	6/18
2	6	RCS	6/6	6/6	6/36	6/60
3	5	RCS	6/6	6/6	6/24	6/24
4	4	LCS	6/9	6/12	6/36	6/60
5	4	LCS	6/6	6/9	6/36	6/24
6	6	LCS	6/9	6/12	4/60	2/60
7	12	RCS	6/6	6/6	6/18	6/18
8	5	RCS Congenital nystagmus	6/18	6/18	2/60	2/60
9	6	Left aphakia c CL	6/6	6/6	6/36	6/36
10	5	LCS	6/6	6/6	<1/60	<2/60
11	6	RCS	6/9	6/12	6/18	6/24
12	7	LCS	6/6	6/9	6/18	6/24
13	6	LCS	6/6	6/9	6/18	6/12
14	6	RCS	6/6	6/6	6/18	6/24
15	5	Left microtropia	6/9	6/9	6/18	6/18
16	4	Left anisometropia	6/9	6/9	6/60	6/36
17	6	LCS	6/9	6/9	6/18	6/18
18	4	LCS L/R	6/6	6/9	2/60	<2/60
19	6	LCS	6/6	6/9	6/12	6/12
20	6	LCS	6/6	6/9	6/36	6/24
21	5	LCS	6/6	6/9	6/18	6/24
22	3	RCS	6/12	6/18	6/60	6/36
23	5	RCS	6/6	6/9	6/24	6/18
24	8	LCS	6/6	6/9	6/24	6/18
25	3	RCS	6/9	6/9	6/18	6/18

LDS=left divergent squint. LCS=left convergent squint. RCS=right convergent squint. c CL=with contact lens. L/R=left over right.

amblyopia, but there is considerable evidence that it is not simply blurring of the image.^{9 10 17} Strabismic amblyopes and neonates both behave similarly when faced with vernier targets.^{12 15-17}

Grating acuity may depend on the smallest size of receptor field that shows functionally effective contrast sensitivity.^{7 19} Vernier acuity requires detection of offsets and may depend more on the density of receptor fields than on the size of them.²⁰ It deteriorates two to three times faster than grating acuity in the normal retinal peri-

phery as a function of retinal eccentricity,^{17 21} and it is also degraded more than grating acuity in strabismic amblyopia.¹⁵⁻¹⁷ The primary deficits in strabismic amblyopia cannot be mimicked by blur and cannot be explained solely by filtering properties. Rather they are both quantitatively and qualitatively similar to normal peripheral vision. The primary deficits in anisometropic amblyopia can be accounted for by the spatial filtering and contrast response properties of the visual system, while the deficits in strabismic amblyopia are mainly a consequence of spatial undersampling as in neonatal vision.¹⁷ Since vernier and grating acuities reflect different aspects of visual sampling and early processing, the comparison between them within individual infants may serve as a significant critical test during the first year of life.²⁰ Because of the undersampling concept perhaps our vernier type targets may be more clinically useful in early infancy and strabismic amblyopia than preferential looking gratings.

Our targets cannot possibly be measuring true vernier hyperacuity, as no gross hyperacuity values are obtained in comparison with Snellen acuity in amblyopic children. There appears to be no overestimate of vision produced by our moving targets. Indeed it has been shown that there is no significant difference between visual acuities with static and phase alternated targets.²²

The drum method of vision testing has been recognised as offering one of the best chances of rapid and reliable assessment of vision in small children if a better target could be devised. We know that the Catford apparatus is robust and has stood the test of time in mechanical reliability.

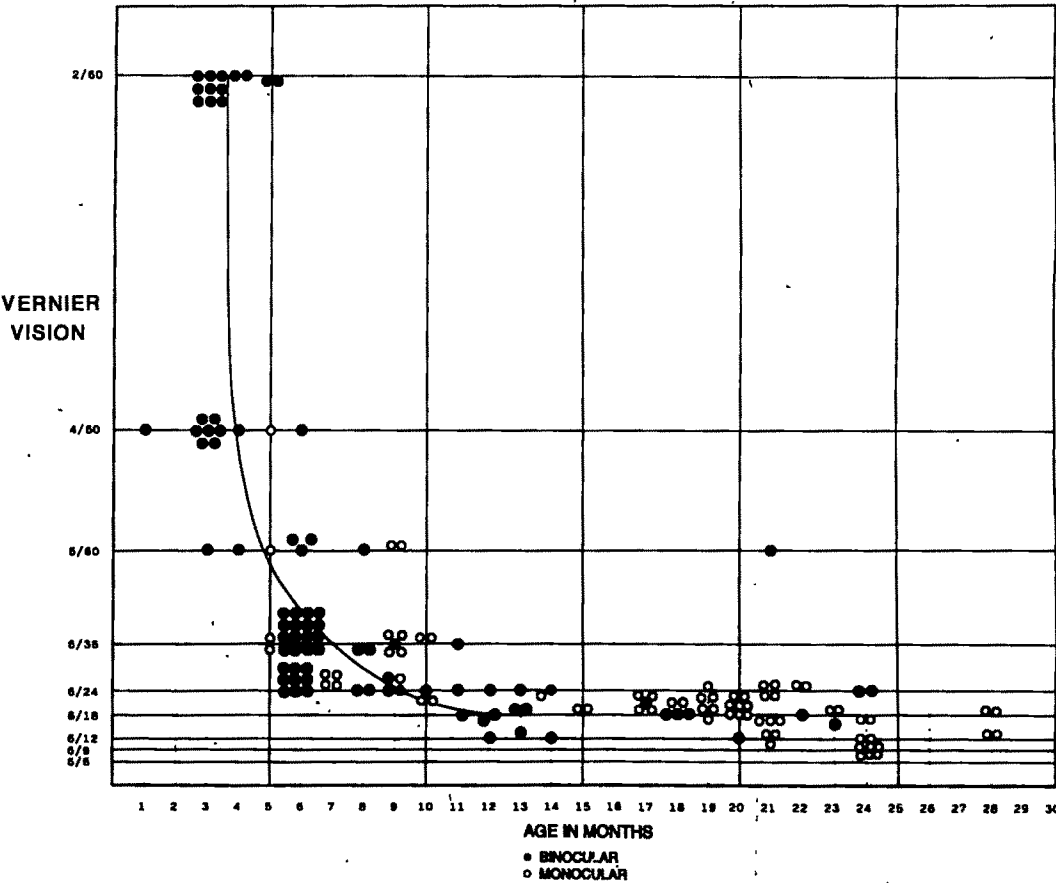


Figure 4 120 normal infants: development of 'vernier' vision.

We know that most orthoptists are familiar with the apparatus and find it simple, quick, and easy to use in the clinical situation. We believe that we have developed a target for the Catford drum which gives a clinically good and useful visual value in young children and indeed in older children who cannot be formally tested by other quick, easy methods in the clinical situation. The strips are cheap and replaceable when soiled; they are easily attached to the drums by double sided sticky tape or glue.

We have found a knowledge of our vernier vision in normal babies, in babies with squint, in anisometropia and some pathological conditions is clinically useful. We can certainly record the improvement in vision in the amblyopic eye of preverbal children after occlusive therapy, and we are confidently able to discharge from follow-up children with pseudosquint who have been found to have equally good vision in each eye much earlier than previously.

We are sure that there will be exceptions and difficult cases to assess with our targets, especially some cases with ocular motility problems, but we have certainly been able to record accurate visions of some children with congenital nystagmus.

We do not pretend to understand fully the physiological reasons for our targets giving a clinically reasonable correlation with Snellen targets, but we believe this method of visual assessment warrants further investigation to establish the true extent of its potential.

We thank Mr G V Catford for his help and encouragement in this project.

- 1 Catford GV, Oliver A. Development of visual acuity. *Arch Dis Child* 1973; 48: 47-50.
- 2 Atkinson J, Braddick O, Pimm-Smith E, Ayling L, Sawyer R. Does the Catford drum give an accurate assessment of acuity? *Br J Ophthalmol* 1981; 65: 652-6.
- 3 Khan SG, Chen KF, Frenkel M. Subjective and objective visual acuity testing techniques. *Arch Ophthalmol* 1976; 94: 2086-91.
- 4 Teller DY, Morse R, Borton R, Regal D. Visual acuity for vertical and diagonal gratings in human infants. *Vision Res* 1974; 14: 1433-9.
- 5 Teller DY. The forced-choice preferential looking procedure: a psychophysical technique for use with human infants. *Infant Behav Dev* 1979; 2: 135-53.
- 6 Atkinson J, Braddick O, Moor K. Development of contrast sensitivity over the first 3 months of life in the human infant. *Vision Res* 1977; 17: 1037-44.
- 7 Banks MS, Salapatek P. Acuity and contrast sensitivity in 1-, 2-, and 3-month-old human infants. *Invest Ophthalmol Vis Sci* 1978; 17: 361-5.
- 8 Gwiazda J, Brill S, Mohindra I, Held R. Infant visual acuity and its meridional variation. *Vision Res* 1978; 18: 1557-64.
- 9 Hess RF, Campbell FW, Greenhalgh T. On the nature of the neural abnormality in human amblyopia; neural aberrations and neural sensitivity loss. *Pflügers Arch* 1978; 377: 201-7.
- 10 Hess RF, Jenkins S. Amblyopia cannot be explained by considering only detection thresholds. *Perception* 1980; 9: 569-76.
- 11 Katz B, Sireteanu R. Teller acuity card test. *Klin Monatsbl Augenheilkd* 1989; 195: 17-22.
- 12 Shimojo S, Birch EE, Gwiazda J, Held R. Development of vernier acuity in infants. *Vision Res* 1984; 24: 721-8.
- 13 Davson H. *Physiology of the eye*. 2nd ed. London: Churchill 1963: 168.
- 14 Westheimer G. The spatial sense of the eye. *Invest Ophthalmol Vis Sci* 1979; 18: 893-912.
- 15 Levi DM, Klein SA. Hyperacuity and amblyopia. *Nature* 1982; 298: 268-70.
- 16 Levi DM, Klein SA. Differences in vernier discrimination for gratings between strabismic and anisometric amblyopes. *Invest Ophthalmol Vis Sci* 1982; 23: 398-407.
- 17 Levi DM, Klein SA. Vernier acuity, crowding and amblyopia. *Vision Res* 1985; 25: 979-91.
- 18 Ray WA, O'Day DM. Statistical analysis of multi-eye data in ophthalmic research. *Invest Ophthalmol Vis Sci* 1985; 26: 1186-8.
- 19 Atkinson J, Braddick O, Braddick F. Acuity and contrast sensitivity of infant vision. *Nature* 1974; 247: 403.
- 20 Shimojo S, Held R. Vernier acuity is less than grating acuity in 2- and 3-month-olds. *Vision Res* 1987; 27: 77-86.
- 21 Westheimer G. The spatial grain of the perifoveal visual field. *Vision Res* 1982; 22: 157-62.
- 22 Dobson V, Teller DY, Belgum J. Visual acuity in human infants assessed with stationary stripes and phase-alternated checkerboards. *Vision Res* 1978; 18: 1233-8.

Does the pilocarpine phenylephrine provocative test help in the management of acute and subacute angle closure glaucoma?

P K Wishart

Abstract

The pilocarpine phenylephrine provocative test (PPPT) has been described as a highly sensitive method to identify eyes suffering from or at risk of angle closure glaucoma (ACG).¹ This paper reports on average 10 years follow-up of the outcome of cases of primary acute ACG and subacute ACG in which the management was determined by the result of the PPPT – a positive result indicating the need for a peripheral iridectomy, a negative result conservative treatment. In spite of a negative PPPT the fellow eyes of cases of acute ACG treated conservatively had a high rate (40%) of development of ACG. Similarly, in eyes with a history of subacute ACG with a negative PPPT, ACG developed at some stage during the follow-up in 60%. Peripheral iridectomy alone resulted in normal intraocular pressure in 63% of eyes that had suffered an attack of acute ACG. In hypertensive eyes that presented with subacute ACG, however, only one eye became normotensive following peripheral iridectomy alone. In the subacute ACG group a positive PPPT was closely related to the presence of glaucomatous optic disc damage.

These results indicate that the PPPT lacks sensitivity in detecting eyes at risk of angle closure glaucoma, and a positive result is likely in eyes with damaged outflow that will not respond to peripheral iridectomy.

Angle closure glaucoma (ACG) is believed to occur when a relative degree of pupil block leads to iridocorneal contact and subsequent closure of the trabecular meshwork by the peripheral iris. Primary ACG occurs in eyes with shallow anterior chambers (AC) and narrow angles.² Many more people have narrow angles and shallow ACs than develop ACG, and the risk of the individual is difficult to assess.³ The symptoms and signs of a case of acute ACG – pain and blurred vision, corneal oedema, very high intraocular pressure (IOP), and a mid-dilated fixed, oval pupil – are well recognised, and treatment is directed at the relief of pupil block.⁴ Patients with shallow ACs presenting with a history suggestive of an attack of subacute ACG may present more of a diagnostic challenge. The differential diagnosis includes all causes of ocular or periorbital pain, but in an eye with raised pressure and a narrow angle the clinician is likely to think first of subacute ACG. The desire for an objective test that will indicate the presence of angle closure or identify those eyes especially at risk has led to the development of provocative tests. This paper examines the use of the

pilocarpine phenylephrine provocative test (PPPT) to identify those eyes at risk of ACG and those eyes in which raised IOP was due to an angle closing mechanism.

Patients and methods

Between 1974 and 1986 patients presenting with acute or subacute ACG were entered into a longitudinal study. In cases of acute ACG with a fixed, semidilated pupil, corneal oedema, ocular pain, and IOP greater than 45 mmHg surgical peripheral iridectomy was performed once the IOP had been lowered by medical therapy. All eyes with signs and/or a history of symptoms suggestive of subacute ACG and the fellow eye of cases of acute ACG were treated by performing a PPPT soon after presentation. If negative, the test would be repeated at approximately three months after presentation and thereafter at yearly intervals. If at a later date the test became positive – and a rise of 8 mmHg in the presence of a closed angle was taken as a positive result – a peripheral iridectomy would be performed. Miotics were not prescribed prophylactically for those eyes with a negative PPPT, but a raised IOP was treated with timolol and/or pilocarpine. Since 1987 all patients in this study was examined by Zeiss four-mirror indentation gonioscopy to identify peripheral anterior synechiae of the AC angle. Axial anterior chamber depth was measured with the Haag-Streit pachymeter, and a full slit-lamp examination of the anterior and posterior segments of both eyes was performed.

Results

One hundred and fifty-eight patients with acute or presumed subacute ACG were entered into the study, but 18 were either dead or lost to follow-up by December 1986. In seven cases the ACG was secondary to an event such as central retinal vein occlusion or intumescent lens, and these patients have been excluded from this report. Two patients with a diagnosis of subacute ACG are excluded, as one patient's symptoms were later shown to be due to migraine, and in the other presentation was following a rise in pressure due to the instillation of mydriatics for a routine fundus examination.

One hundred and four patients presented with acute ACG. Thirty two patients (64 eyes) with at least two of the following symptoms or signs of subacute ACG – pain, blurring, spectral haloes, and raised IOP – were entered into the study and followed up. The demographic details of these patients are given in Fig 1 and 2 and the

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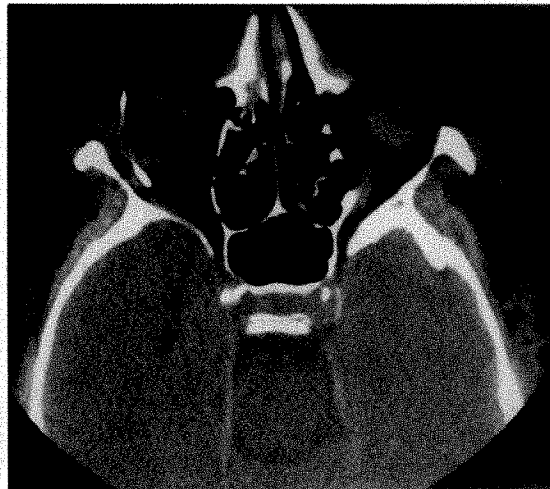
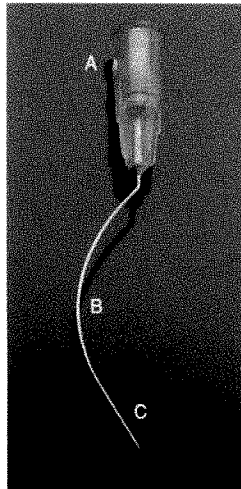
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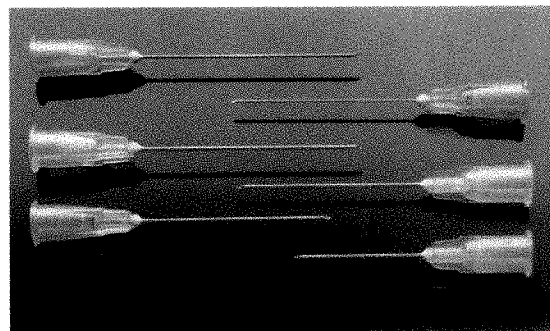


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[Straus], positioned for
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length of the eye is 22.5mm.
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temporally. The straight
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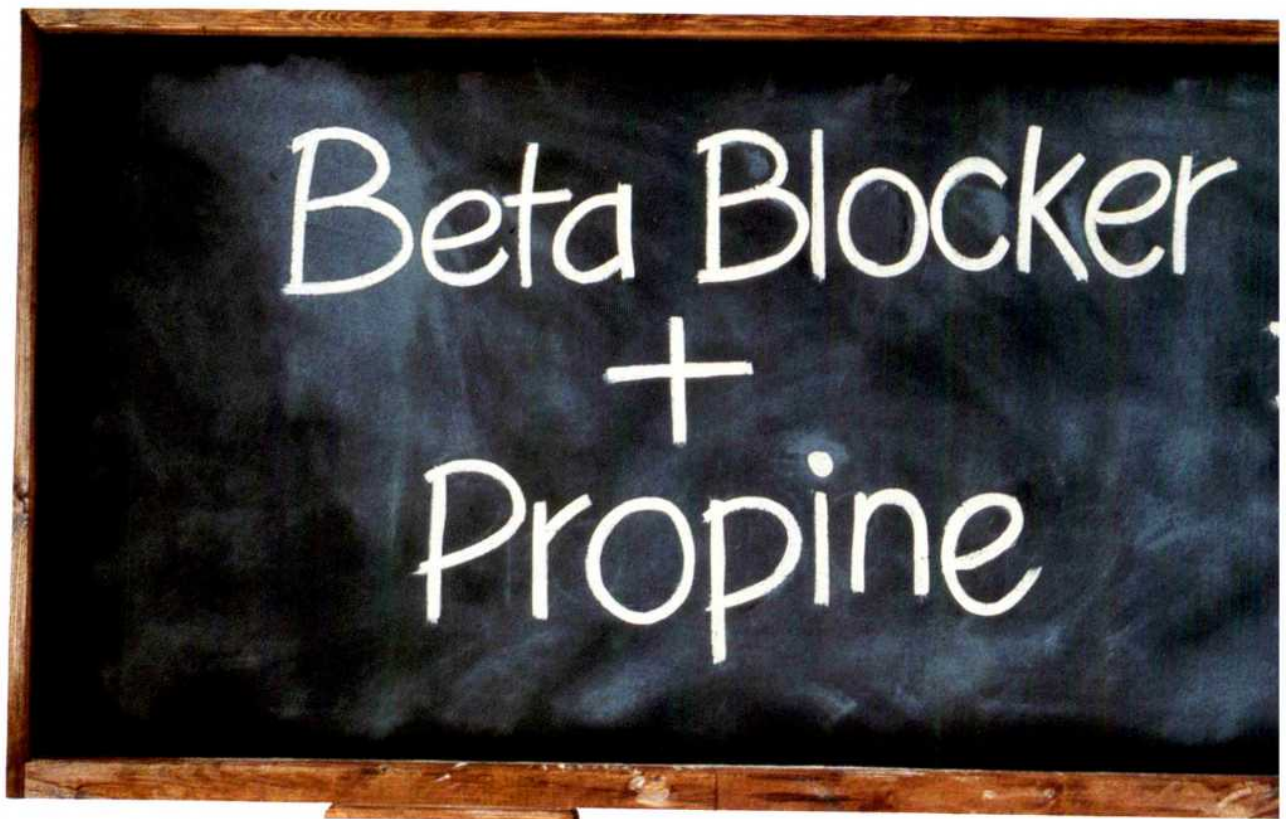
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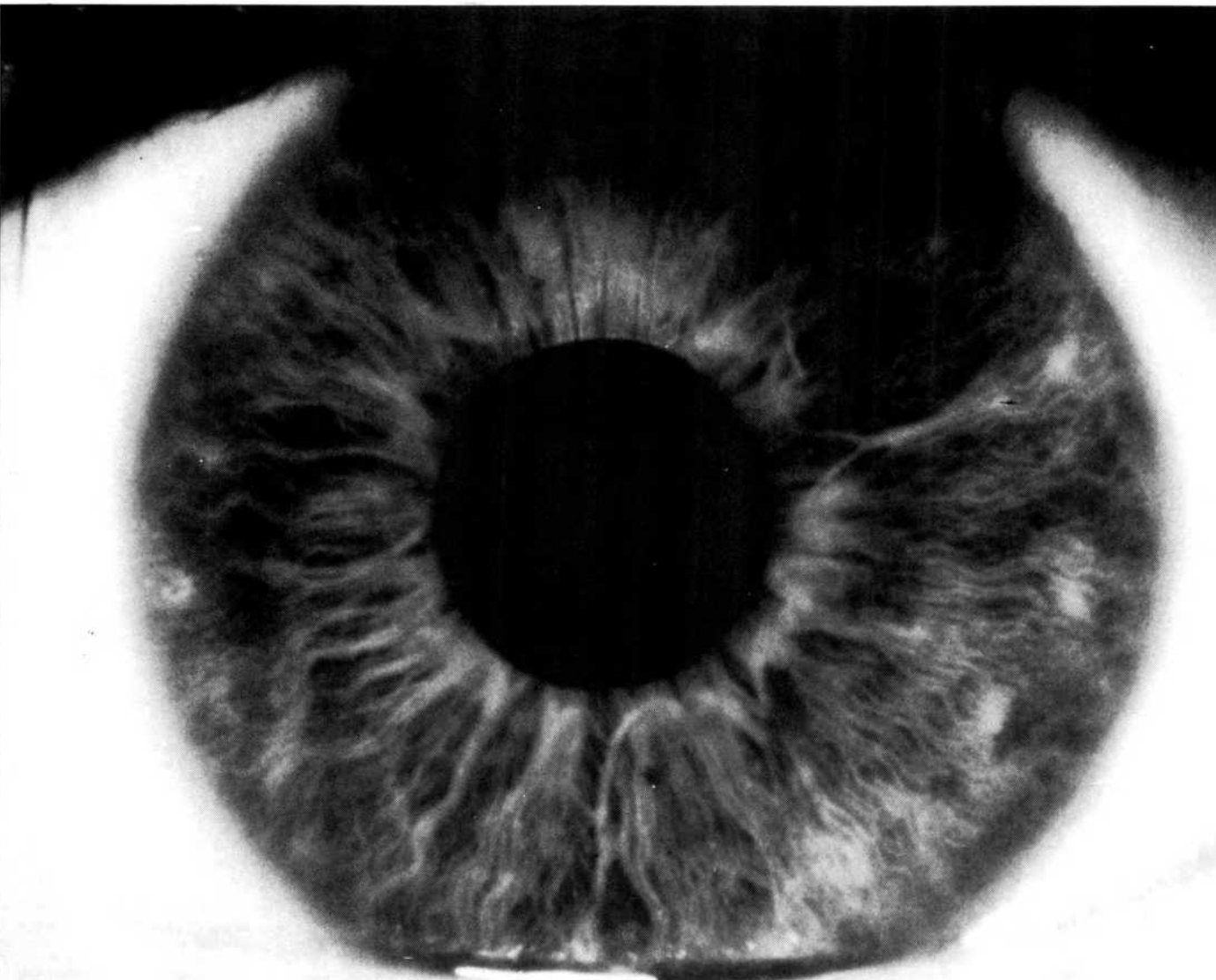
a prodrug of adrenaline. Its lipophilic nature facilitates penetration into the anterior chamber where it is hydrolysed to the active substance. Propine is a more efficient way of delivering adrenaline with fewer side-effects than associated with conventional therapy. Unlike cholinergic agents, dipivefrin has little or no effect on pupil size or accommodation, so the blurred vision and night blindness associated with miotics do not occur with Propine. **Basic NHS cost:** 5 ml—£4.29; 10 ml—£4.89. **Product licence number** 0426/0040. **Date of preparation** February 1991.

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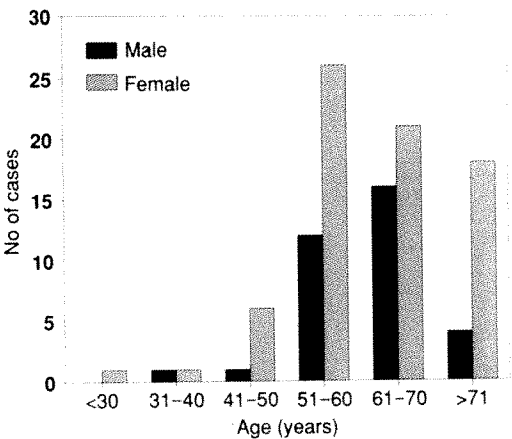


Figure 1 Patients with acute ACG: age in years.

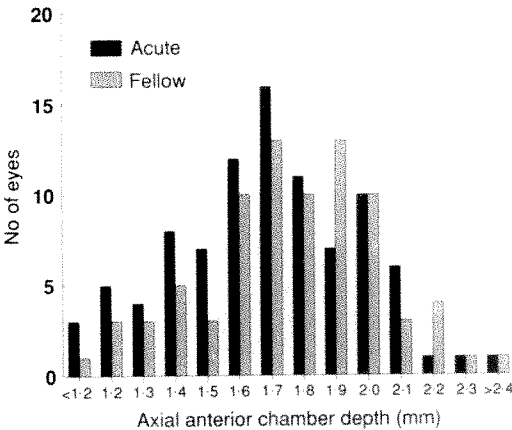


Figure 3 Distribution of axial ACD in cases of acute ACG.

distribution of axial anterior chamber depths in Fig 3 and 4.

In common with other studies acute ACG was seen more commonly in women than men (74 females to 30 males). An onset in the winter months (October to March) was more common in cases of acute ACG, with 75 in winter and 29 in summer. In the patients with subacute ACG the proportion of females to males was (20: 12), with 14 winter onsets to 18 summer onsets. The average age was 61.7 (SD 8.7) years in acute ACG patients and 57.45 years (SD 8.94) in subacute ACG patients. In acute ACG eyes the mean anterior chamber depth was 1.72 mm, (SD 0.297), in fellow eyes 1.765 mm (SD 0.293), and in subacute ACG 1.91 mm (SD 0.23 mm).

The mean follow-up of the patients in the acute ACG group was 9.95 years (SD 5.66), and in the subacute ACG group 10.7 years (SD 4.02).

By the end of the follow-up period, of the 104 eyes that had suffered acute ACG one eye had been enucleated because it was blind and painful. Twenty-six eyes had raised IOP requiring long-term hypotensive medication, and in a further 12 eyes the pressure was normal after successful filtering surgery. Peripheral iridectomy alone resulted in a normal IOP in 65 (63%) of the eyes that had suffered an attack of acute ACG.

In the acute ACG patients, of the 104 fellow eyes 37 showed a positive PPPT. In 20 eyes this test was positive within 10 days of presentation, and in a further 13 eyes the test was positive within the first year following presentation. In the remaining four fellow eyes the PPPT

became positive between one and 10 years after presentation. Of these 37 fellow eyes with a positive PPPT 34 underwent a prophylactic surgical peripheral iridectomy, one was treated by lens extraction, and two had prophylactic argon laser iridotomies performed. The 35 eyes that were treated surgically had a satisfactory outcome in that no eye subsequently developed angle closure glaucoma or required further surgery. Both eyes that underwent argon laser iridotomy developed raised IOP, and the laser iridotomies were judged to be non-patent. Because of the raised IOP and the laser-induced intraocular inflammation both these eyes underwent surgical trabeculectomy. Prior to their prophylactic surgical peripheral iridectomy nine of these fellow eyes had a mild increase of the IOP (five eyes being in the group that had a positive PPPT within 10 days of presentation, and four in the group whose PPPT became positive later). The IOP remained raised in all these nine eyes postoperatively and was treated with topical medication. In only one eye was glaucomatous damage to the optic disc observed by the end of the follow-up period. The other eyes were judged to be suffering from ocular hypertension, while their optic discs remained normal.

In four of the remaining 67 fellow eyes a PPPT induced an attack of acute angle closure glaucoma unresponsive to 24 hours of medical therapy and requiring surgery for control. Four cases

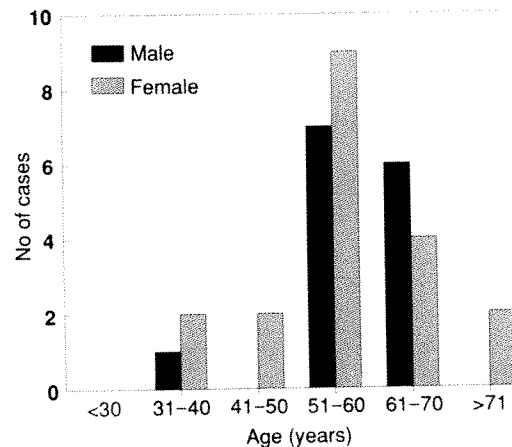


Figure 2 Patients with subacute ACG: age in years.

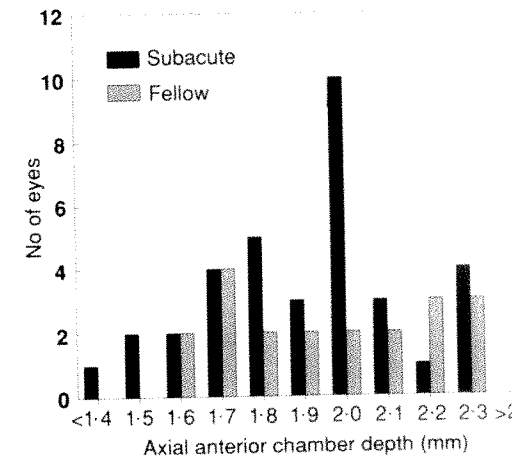


Figure 4 Distribution of axial ACD in cases of subacute ACG, fellow eye being one with a negative PPPT.

presented with bilateral acute ACG, and one developed acute ACG while waiting for PPPT of the fellow eye. One fellow eye with an anterior chamber depth of 2.7 mm was thought not to be at risk of ACG.

Fifty six at risk fellow eyes in the acute ACG group had consistently negative PPPTs. During two to 15 years (average 10 years) of follow-up despite a negative PPPT, 14 spontaneously developed an attack of acute ACG, and three eyes developed symptoms of subacute ACG. A further five eyes had persistently raised IOP, and Zeiss four-mirror indentation gonioscopy revealed extensive synechial closure of the superior anterior chamber angle. These eyes were asymptomatic and were therefore cases of creeping ACG as described by Lowe.⁵ Thus 22 of 56 (40%) at risk fellow eyes with a negative PPPT developed closed-angle glaucoma.

In the subacute ACG patients 30 eyes had a positive PPPT, 27 of these within the first two months of presentation, and underwent peripheral iridectomy. Twenty of these eyes with positive PPPT had a raised IOP at the time of presentation, and 10 were normotensive. All 10 normotensive eyes had normal discs, but only seven of the hypertensive eyes had normal discs. The other 13 eyes in the hypertensive group had advanced glaucomatous optic disc damage.

In those 20 hypertensive eyes with a positive PPPT, peripheral iridectomy resulted in a normal IOP without further treatment only in one eye. In a further two eyes it improved control of the IOP. In the other 17 eyes the IOP was not lowered by the operation. Five eyes required trabeculectomy, and 11 had progressive, severe visual loss due to glaucomatous optic disc damage by the end of the follow-up period. Nine eyes developed cataracts.

One eye in the patients with suspected subacute ACG is excluded from the analysis because it had suffered previous angle recession, and therefore 33 eyes in the subacute ACG group had negative PPPTs, of which 18 were hypertensive at the time of presentation. Thirty two of these negative PPPT eyes had normal optic discs, while one showed advanced glaucomatous damage.

Of these 33 remaining eyes followed up with yearly negative PPPTs six spontaneously developed an attack of acute ACG, and nine developed signs and symptoms of subacute ACG. Five eyes with persistently raised IOP were seen to have extensive closure of peripheral anterior synechial of the superior anterior chamber angle and were therefore judged to have developed creeping ACG.⁶

Four eyes in the negative PPPT group developed cataracts, but all these occurred in eyes that had suffered a spontaneous attack of acute ACG. Thus 20 of the 33 (60%) eyes at risk with a negative PPPTs developed ACG.

Discussion

Observation of a large group of patients at risk of developing ACG was considered to be justified by means of the PPPT to identify the ones at risk and those eyes in which the raised IOP was due to an angle closing mechanism.¹⁶ Views differ on the reliability of provocative tests. Spaeth⁷ has

criticised all pharmacological provocative tests as being unphysiological, especially the PPPT, which induces a situation never occurring in life – that of maximum sympathetic and parasympathetic forces operating simultaneously in the eye. He recommends, if any is to be used, the dark-room test, which has been unfavourably compared to the PPPT by Mapstone,⁸ who reports the PPPT as being 93% sensitive for detection and prediction of ACG.¹

Although many ophthalmologists consider that the risk of ACG in a fellow eye is so great that a prophylactic or laser iridotomy should always be performed,^{9,10} others have disagreed, preferring reliance on provocative tests to determine which fellow eye should undergo surgical peripheral iridectomy.^{11,12} For patients with acute ACG most surgeons nowadays perform a prophylactic laser iridotomy on fellow eyes owing to the relative ease and safety of this procedure. However, both argon and YAG laser iridotomy may fail to relieve pupil block.¹³ Usually this occurs as a result of closure of the iridotomy by the reparative process of pigment epithelial proliferation.¹³ A very small iridotomy in a thick iris may also be unable to permit sufficient flow of aqueous from the posterior to the anterior chamber to break the pupil block.¹³ Some authors have recommended that provocative testing should be performed following laser iridotomy,^{14,15} and a recent paper has suggested the use of the PPPT to ensure adequacy of the iridotomy.¹⁶

The PPPT has been reported as a highly sensitive method of detecting the presence of ACG and predicting whether an eye is likely to suffer from it.¹ In a paper which included cases of acute ACG, subacute ACG, and chronic ACG Mapstone reported that the risk of ACG occurring more than 5 years after an attack of ACG was nil.¹ Further follow-up of these cases with primary symptomatic ACG showed that spontaneous acute ACG can occur more than five years after the initial attack (three eyes), and 40% of fellow eyes developed ACG not detectable by the PPPT. The long-term sensitivity of the PPPT must therefore be only 61%, a relatively low figure considering that fellow eyes are known to be at high risk of angle closure glaucoma.^{17,18}

In those eyes with a history of subacute ACG a negative PPPT was associated with the later development of ACG in 60%. It is important to note also that only one eye with a damaged optic disc had a negative PPPT, while the other 14 (93%) eyes with glaucomatous discs had positive PPPTs. If these eyes are analysed with respect to raised IOP, of 21 eyes with raised IOP and a positive PPPT 14 (66%) had severe disc damage, while of 18 hypertensive eyes with a negative PPPT only one eye (6%) showed disc damage. Thus an eye with raised IOP and a damaged optic disc is 10 times more likely to have a positive than a negative PPPT.

Peripheral iridectomy alone did not result in a normal IOP in any hypertensive eye with optic disc damage, yet 93% of such eyes had a positive PPPT. Clearly, if a PPPT in an eye with disc damage is positive and a peripheral iridectomy is performed, the IOP is unlikely to be lowered. There seems little point, therefore, in performing

the PPPT in such eyes. From the findings in this study a positive result does not necessarily mean that an angle closing mechanism has been identified; it may simply occur because an already damaged outflow mechanism is unable to cope with pigment release, relative degree of induced pupil block, or the shallowing of the anterior chamber – all of which occur as a result of the PPPT.^{19, 20} The PPPT therefore does not specifically identify that an angle closing mechanism is responsible for the raised IOP.

In contrast, peripheral iridectomy alone resulted in a normal IOP in 63% of cases of acute ACG in this study, which is similar to the 72% success rate reported by Playfair and Watson⁹ and the 69% success rate reported David *et al*.²¹ for acute ACG.

In this study prophylactic surgical peripheral iridectomy performed on those fellow eyes that had a positive PPPT was successful in preventing ACG. In the two fellow eyes where an attempt to create a prophylactic argon laser iridotomy failed, subsequent intraocular inflammation and raised IOP necessitated filtering surgery. However, at that time argon laser iridotomy was in its infancy, and the poor results represent failure of technique. With more modern techniques²² and newer lasers,^{23, 24} laser iridotomy is a widely accepted and very successful alternative to surgical peripheral iridectomy.

Finally, the PPPT itself has risks. Following a PPPT four fellow eyes of the acute ACG group and three from the subacute ACG developed an acute attack of ACG, which in 50% of cases required surgery to break the attack.

CONCLUSIONS

In any eye with primary ACG, a prophylactic surgical iridectomy or laser iridotomy should be performed on the fellow eye to prevent the development of ACG. The PPPT is neither a sensitive nor a specific test and is not helpful in the diagnosis or management of ACG.

I thank Mrs C Owen for technical and administrative help.

- 1 Mapstone R. The fellow eye. *Br J Ophthalmol* 1981; 65: 410–3.
- 2 Shields MB. Primary angle-closure glaucoma. *textbook of glaucoma* Baltimore: Williams and Wilkins 1987: 165–85.
- 3 Spaeth GL. The normal development of the human anterior chamber angle: a new system of descriptive grading. *Trans Ophthalmol Soc UK* 1971; 91: 709–39.
- 4 Curran EJ. A new operation for glaucoma involving a new principle in the aetiology and treatment of chronic primary glaucoma. *Arch Ophthalmol* 1920; 49: 131–40.
- 5 Lowe RF. Primary creeping angle-closure glaucoma. *Br J Ophthalmol* 1964; 48: 544–50.
- 6 Mapstone R. Narrow angle glaucoma. *Doc Ophthalmol Proc Ser* 1980; 22: 185–93.
- 7 Spaeth GL. *Ophthalmic surgery: principles and practice*. Philadelphia: Saunders, 1982: chapter 10: 301–60.
- 8 Mapstone R. Angle-closure mechanisms in glaucoma. *Sem Ophthalmol* 1986; 1: 35–40.
- 9 Playfair TJ, Watson PG. Management of acute primary angle-closure glaucoma: a long-term follow-up of the results of peripheral iridectomy used as an initial procedure. *Br J Ophthalmol* 1979; 63: 17–22.
- 10 Krupin T, Mitchell KB, Johnson MF, Becker B. The long-term effects of iridectomy for primary angle-closure glaucoma. *Am J Ophthalmol* 1979; 85: 506–9.
- 11 Floman N, Berson D, Landau L. Peripheral iridectomy in closed angle glaucoma – late complications. *Br J Ophthalmol* 1977; 61: 101–4.
- 12 Hyams SW, Friedman Z, Keroub C. Fellow eye in angle-closure glaucoma. *Br J Ophthalmol* 1974; 59: 207–10.
- 13 Wishart PK, Hitchings RA. Nd: YAG and dye laser iridotomy – a comparative study. *Trans Ophthalmol Soc UK* 1986; 105: 521–8.
- 14 Quigley HA. Long-term follow-up of laser iridotomy. *Ophthalmology* 1981; 88: 218–24.
- 15 Saunders DC. Acute closed-angle glaucoma and Nd-YAG laser iridotomy. *Br J Ophthalmol* 1990; 74: 523–5.
- 16 Gray RH, Hoare Nairne J, Ayliffe WHR. Efficacy of Nd-YAG laser iridotomies in acute angle closure glaucoma. *Br J Ophthalmol* 1989; 73: 182–5.
- 17 Edwards RS. Behaviour of the fellow eye in acute angle-closure glaucoma. *Br J Ophthalmol* 1982; 66: 576–9.
- 18 Lowe RF. Acute angle-closure glaucoma. The second eye: an analysis of 200 cases. *Br J Ophthalmol* 1962; 46: 641–50.
- 19 Mapstone R. Mechanisms in ocular hypertension. *Br J Ophthalmol* 1979; 63: 325–30.
- 20 Mapstone R. Acute shallowing of the anterior chamber. *Br J Ophthalmol* 1981; 65: 446–51.
- 21 David R, Tessler Z, Yassur Y. Long-term outcome of primary acute angle-closure glaucoma. *Br J Ophthalmol* 1985; 69: 261–2.
- 22 Wise JB. Iris sphincterotomy, iridotomy, and synechiotomy by linear incision with the argon laser. *Ophthalmology* 1985; 92: 641–5.
- 23 Schwartz LW, Moster MR, Spaeth GL, Wilson RP, Poryzees E. Nd: YAG laser iridotomy in glaucoma associated with closed or occludable angles. *Am J Ophthalmol* 1986; 102: 41–4.
- 24 Pollack IP, Robin AL. A comparison of Nd: YAG and argon laser iridotomy. *Ophthalmology* 1984; 91: 1011–6.

Medial canthal resection: an effective long-term cure for medial ectropion

T J Sullivan, J R O Collin

Abstract

The results of 37 medial canthal resection procedures performed for the correction of severe paralytic or involutional medial ectropion are presented with an average follow-up of 5.4 years. Epiphora was improved in 33 out of the 37 cases and all but one patient had an anatomically improved lid-globe apposition, medial canthal angle, and postero-fixation of the medial canthus. These results confirmed the long-term value of the operation.

Adequate treatment of severe medial ectropion with medial canthal tendon laxity is difficult. Problems in surgery arise because the medial canthal tendon has a superficial and deep head, the posterior attachment of which is difficult to recreate. Further, the medial canthal tendon overlies the lacrimal canaliculus, and surgery to the medial canthal tendon may interfere with lacrimal drainage.

Various procedures¹⁻³ have been described for medial ectropion. However, when there is a laxity of the medial canthal tendon, they will not improve epiphora, because the medial canthal tendon is not shortened sufficiently or postero-fixed adequately.

McCord⁴ described a canaliculostomy procedure when treating neoplastic disease of the medial lower lid. Crawford *et al*⁵ then described a procedure for the correction of paralytic ectropion. This procedure involves resection of the medial canthal structures with a horizontal lid shortening, reconstituting the posterior limb of the medial canthal tendon with a permanent suture, and marsupialisation of the cut inferior canaliculus into the conjunctival sac of the lower fornix.

Since the original description for paralytic ectropion 37 procedures on 29 patients have been performed, not only for paralytic ectropion but also for involutional medial ectropion associated with medial canthal tendon laxity.

This paper reviews our long-term results from 37 medial canthal tendon resections. Factors to be considered for an acceptable result include relief from epiphora, elimination of exposure, and satisfactory cosmesis.

Subjects and methods

The records of 29 patients who had undergone medial canthal resection surgery at Moorfields Eye Hospital were reviewed retrospectively. There was a total of 37 procedures, which were bilateral in eight patients. In 17 patients the aetiology was paralytic (Figs 1A, B) and in 12 involutional (Figs 2A, B). Sixteen were male and 13 female, with a mean age of 67.3 years at



Figure 1A Left paralytic ectropion (note brow droop).

operation. All the patients except one complained of epiphora. Seven patients also had symptoms of exposure; all of these had paralytic ectropions. Most patients had poor cosmesis, and this was more of a problem in the paralytic group.

In addition to a routine, full ocular examination the preoperative assessment included lid position, lid laxity, medial and lateral canthal tendon laxity, and patency and function of the lacrimal drainage apparatus. The indication for medial canthal tendon resection was a severe medial ectropion associated with marked laxity of the medial canthal tendon, where it was considered a simpler operation would fail or had already failed to achieve an acceptable result.

The operation was performed under either general or local anaesthesia. The lower lid margin was grasped immediately lateral to the punctum and pulled laterally. The lid was cut vertically through its full thickness (Fig 3a), including the medial canthal tendon and the inferior canaliculus, just lateral to the caruncle. Although the canaliculus was cut in this step, it was important to retain as much of it as possible for its later marsupialisation by placing a probe in the canaliculus and moving the scissors laterally after the initial vertical incision had been made through the skin and conjunctiva. The conjunctival aspect of this incision was continued retrogradually (Fig



Figure 1B Left paralytic ectropion 18 months after medial canthal resection.

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Figure 2A Bilateral involutational ectropion.



Figure 2B Bilateral involutational ectropion 12 months after medial canthal resections.

3b). Blunt ended scissors were then used to enter this retrobulbar plane. The tissues were spread with the blades tangential to the globe and directed to the posterior lacrimal crest. This avascular space was enlarged, and the medial orbital wall was exposed with two small malleable retractors.

Both half circle needles of a double armed 5-0 non-absorbable suture were placed through the periosteum of the posterior lacrimal crest, one at the level of the medial canthal tendon and one 2 mm higher (Fig 3b, c). The lateral edge of the cut lid margin was then drawn towards the posterior lacrimal crest to assess the amount of horizontal lid shortening required. The lid was then shortened, and the two ends of the non-absorbable suture were placed through the upper and lower aspects of the cut tarsal plate. These were not tied at this stage. The canalicular stump was cut to give small anterior and posterior flaps, which were used to fashion a new ostium. The anterior flap was sutured high up on the cut edge of the tarsus with two 8-0 absorbable sutures (Fig 3d). The lid margin was held medially as the permanent suture was tied to approximate the lower lid against the globe and recreate the

medial canthal angle. The lid margin and skin were then sutured with 6-0 silk (Fig 3d). It was occasionally necessary to resect the lower half of the caruncle if it prolapsed forward excessively. The eye was padded for 48 hours to minimise postoperative swelling. Skin sutures were removed five days postoperatively, and the lid margin suture was left for 10 days.

When the operation was originally described,⁵ the inferior canalicular remnant and the superior canaliculus were intubated with silicone tubing and the tube was left in situ for three to six months. We found that this was not necessary to achieve a patent lacrimal drainage system and no longer routinely intubate.

After the operation the patients were assessed subjectively and objectively for epiphora and exposure. Cosmesis was assessed subjectively, and by comparing pre- and postoperative appearances and anatomical lid-globe apposition. Initially all the patients underwent a post-operative Jones I test, syringing, and dacryocystogram to assess lacrimal drainage. As it became obvious that the procedure established a patent lacrimal drainage apparatus, formal syringing and the dacryocystogram have been

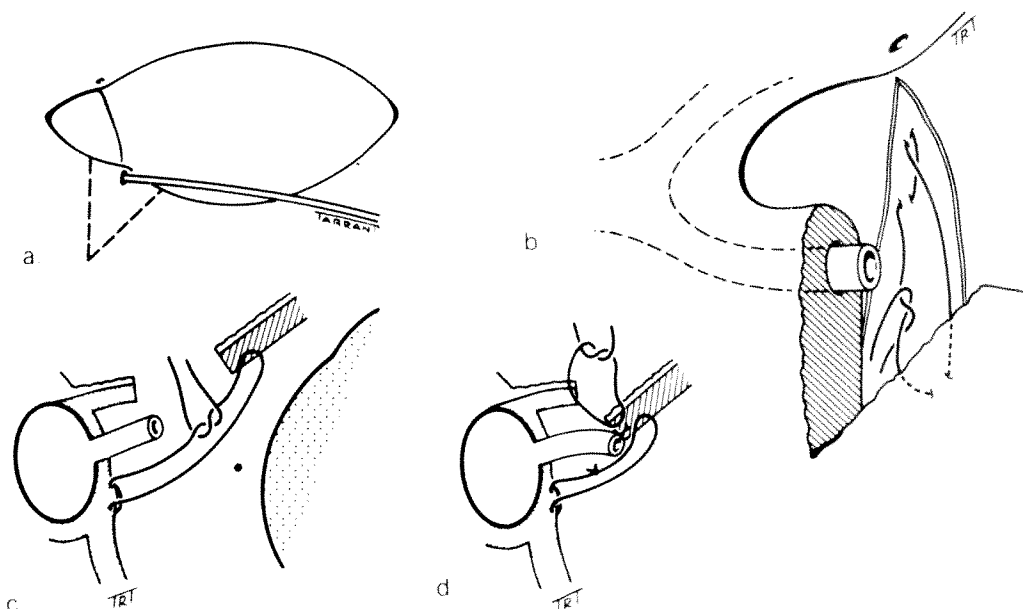


Figure 3 Diagrams of medial canthal resection surgery (taken with permission from JRO Collin: A manual of systematic eyelid surgery. 2nd ed. London: Churchill Livingstone, 1989).

a Anterior view of full thickness lid to be resected. b Anterior view after vertical incisions through lid showing conjunctiva opened behind the plica and posterior fixation suture through periosteum of posterior lacrimal crest. c Superior view of cross section diagram showing posterior fixation suture attached to medial end of resected eyelid. d Superior view of cross sectional diagram showing inferior canaliculus marsupialised into conjunctival sac and attached to superior edge of resected lid with skin closure suture in place.

omitted from the routine postoperative examination.

Follow-up ranged from two months to nine years, mean 5.4 years, allowing valid conclusions to be drawn on the long-term effectiveness of the procedure.

Results

Epiphora was improved by 33 of 37 procedures. It was totally eliminated in 19 of the 37. Of those patients with an improvement in epiphora all said the residual epiphora was mild and acceptable. Of the three patients (four procedures) in whom epiphora was not improved two had pre-existing blockage of the common canaliculus. We have noted this to occur in paralytic ectropion, presumably from disuse secondary to loss of the lacrimal pump function. One of these patients has undergone conjunctivo dacryocystorhinostomy bypass surgery, and the epiphora has been eliminated. The other patient is awaiting lacrimal bypass surgery. In two of these patients the aetiology was paralytic and in the other involutional.

Seven of the 27 patients had exposure problems on presentation. In all of these the aetiology was paralytic. The exposure was eliminated in two, and four of the seven had marked improvement in symptoms and signs with intermittent lubricants. The one patient who did not improve later underwent a lateral tarsorrhaphy with good relief of symptoms.

Twenty one of the 29 patients were recorded in the notes as having felt the cosmetic appearance to be improved by the operation. One patient in whom the aetiology was paralytic felt that her cosmesis was not improved.

Anatomically the lid-globe apposition, medial canthal angle, and postero-fixation of the medial canthus were improved in 28 of 29 patients.

Discussion

The results of this study show that medial canthal tendon resection is an effective, long lasting cure for the problem of severe medial ectropion with medial canthal tendon laxity. Patients with medial ectropion present with epiphora, and the aim of surgery should be to correct the anatomical defect and to relieve the patient's symptoms. In our study epiphora was improved by 33 of 37 procedures performed. No other procedure shortens the tendon effectively, postero-fixates the medial canthus with good lid to globe apposition, and re-establishes a patent lacrimal drainage system.

Attempts to shorten the anterior limb of the medial canthal tendon by plication^{3,6} invariably concertina an already non-functioning canaliculus. Poor lid-globe apposition occurs owing to the anteriorly directed pull on the lid. The Lee medial canthoplasty¹ is a good procedure for inverting the punctum. However, it will not improve functional tear drainage where there is medial canthal tendon laxity, because the canaliculus is still long and lax. The lazy-T procedure² is good for shortening the lid proper and inverting the punctum, especially if the lower lid retractors are caught in the horizontal tarso-

conjunctival closure. When there is medial canthal tendon laxity, it will not alter tear drainage because the surgery is not directed to the anatomical defect.

Two recent papers have addressed the problem of postero-fixation in medial canthal malposition and marked medial ectropion. Jordan *et al*⁷ describe the medial tarsal strip procedure, an adaptation of the lateral tarsal strip.⁸ In this procedure the lid is cut vertically at the medial aspect of the tarsal plate and a tarsal strip fashioned. The medial canthal tissues, including canaliculus, are then excised, and the tarsal strip is sutured, ideally, to the frontal process of the maxilla (if the superior canaliculus is patent) or more posteriorly (if the patient does not have a patent canaliculus or lacrimal sac). This procedure effectively tightens the medial canthal tendon, and if the tarsal strip is sutured posteriorly enough will postero-fixate the medial canthus. In our experience, pull directed from the frontal process of the maxilla does not give as good lid-globe apposition as pull directed from the posterior lacrimal crest, which is the fixation point in our procedure. The medial tarsal strip procedure sacrifices the lower canaliculus, leaving the patient to rely on the superior canaliculus only for drainage. Our procedure confronts the problem of epiphora specifically by marsupialisation of the inferior canaliculus.

Edelstein and Dryden⁹ reconstruct the medial canthal tendon in a complicated procedure, lifting a periosteal flap from the nasal bridge and passing it through a tunnel from the posterior lacrimal crest behind the common canaliculus parallel to the deep head of orbicularis to attach to medial tarsus. They consider possible lacrimal drainage dysfunction from kinking of the canaliculus or damage to the lacrimal sac. Their definition of an acceptable result does not include relief from epiphora. Essentially their procedure is another form of plicating the posterior limb of the medial canthal tendon, for which a good and easier technique has already been described.¹⁰ We use this technique when there is only mild medial canthal tendon laxity, and for this it works well. If there is more medial canthal tendon laxity, then medial canthal resection gives much better results.

Medial canthal resection has three aims, and aspects of the operation are directed to correcting the pathology in each case. Firstly, the medial canthal tendon is shortened directly. Secondly, it is postero-fixated to the posterior lacrimal crest. Thirdly, the cut inferior canaliculus is marsupialised to maintain lacrimal patency.

Following McCord's⁴ description of canaliculostomy, the procedure was first presented by Crawford *et al*⁵ in 1984. It has been used now for over nine years in 37 procedures. Our results presented here show that the procedure deals effectively with the problems of medial ectropion with medial canthal tendon laxity in most cases. The follow-up (mean 5.4 years) shows that its cure is effective in the long term in both paralytic and involutional medial ectropion.

We recommend medial canthal resection with marsupialisation of the inferior canaliculus as the procedure of choice for medial ectropion

associated with moderate to marked medial canthal tendon laxity.

- 1 Lee OS. Operation for correction of everted lacrimal puncta. *Am J Ophthalmol* 1951; **34**: 575-8.
- 2 Smith B. The 'lazy-T' correction of ectropion of the lower punctum. *Arch Ophthalmol* 1976; **94**: 1149-50.
- 3 Stasior OG. Wendell L Hughes Lecture. Complications of ophthalmic plastic surgery and their prevention. *Ophthalmology* 1976; **81** OP: 543-52.
- 4 McCord CD. Canalicular resection and reconstruction by canaliculostomy. *Ophthalmic Surg* 1980; **11**: 440-5.
- 5 Crawford GJ, Collin JRO, Moriarty PAJ. The correction of paralytic medial ectropion. *Br J Ophthalmol* 1984; **68**: 639-41.
- 6 Collin JRO. *A manual of systematic eyelid surgery*. 2nd ed. London: Churchill Livingstone, 1989: 32.
- 7 Jordan DR, Anderson RL, Thiese SM. The medial tarsal strip. *Arch Ophthalmol* 1990; **108**: 120-4.
- 8 Anderson RL, Gordy DD. The tarsal strip procedure. *Arch Ophthalmol* 1979; **97**: 2192-6.
- 9 Edelstein JP, Dryden RM. Medial palpebral tendon repair for medial ectropion of the lower eyelid. *Ophthalmic Plast Reconstr Surg* 1990; **6**: 28-37.
- 10 Collin JRO. *A manual of systematic eyelid surgery*. 2nd ed. London: Churchill Livingstone, 1989: 33.

Acute retinal necrosis syndrome

D S Gartry, D J Spalton, A Tilzey, P G Hykin

Abstract

Acute retinal necrosis (ARN) is a rare syndrome with characteristic fundal appearances which can have devastating effects on vision. We present six cases (nine eyes) seen in the Medical Eye Unit of St Thomas's Hospital over the past six years and discuss the clinical features, aetiology, and management. Our findings support the present consensus that the condition is caused by varicella zoster virus (VZV) or herpes simplex virus (HSV). One of our patients, who was atypical in having common variable hypogammaglobulinaemia, had suffered a widespread zosteriform rash immediately prior to the onset of ARN, while another had suffered a herpes simplex uveomeningoencephalitis. All cases had characteristic confluent peripheral retinal necrosis, and three of the nine eyes developed retinal detachment. Retinal arteritis was a prominent and helpful diagnostic feature in one case. From combining all reports to date of this rare condition it is possible to conclude that ARN is unilateral in 65% of cases.

The acute retinal necrosis syndrome (ARN), first described in Japan in 1971,¹ is characterised by panuveitis, vitritis, vaso-occlusive retinal arteritis, and necrotising retinitis. It is rapidly progressive and often has a devastating effect on vision due to retinal arteritis, retinal necrosis, and rhegmatogenous and traction retinal detachment. According to Culbertson *et al*,^{2,3} the disease is bilateral in 36% of cases. The sexes are affected equally, and patients are usually well, with no significant past medical or ocular history. In 50% to 75% of patients the retina becomes detached within three months of the onset of symptoms.^{2,4,5} In 76% the final visual acuity is less than

6/60, and visual prognosis may also be poor owing to macular oedema and optic nerve damage secondary to vascular insufficiency.

In most cases little or no improvement has been achieved by medical or surgical treatment. As the herpes group of viruses has been implicated,^{2,3,4,6-21} antiviral agents such as acyclovir and gancyclovir have been used in the acute phase,²² with limited success. The retinitis is reduced by these agents but the vitritis is unaffected, and there is still progression to retinal detachment.³

A recent report has, however, documented a milder form of the condition, and the authors²³ suggest that some cases may be subclinical, forming one end of a spectrum of disease. Case 6 below belongs to this category.

Case reports

CASE 1

Mrs M, a 65-year-old patient with susceptibility to upper and lower respiratory tract infections, underwent a lobectomy in 1985 for removal of a lung abscess and prior to surgery was diagnosed as having common variable hypogammaglobulinaemia. No specific treatment was given. In July 1987 she presented with chickenpox, which was treated with antibiotics (pivampicillin 500 mg once a day) and systemic steroids (prednisolone 5 mg once a day orally). Two weeks later she noticed blurring of vision and haloes round lights. Visual acuities were RE 6/18 and LE 6/12. Immunoglobulins were administered intravenously three times a week. Three months later her vision had fallen to 6/60 and 6/18, and a diagnosis of viral retinitis was made. Treatment with topical steroids (dexamethasone eye drops 0.1% four times a day) was instituted, but her vision continued to deteriorate until April 1988, when intravenous acyclovir was begun (450 mg intravenously three times a day for two weeks), and a series of orbital floor steroid injections (beclomethasone 4 mg) were given.

On transfer to St Thomas's Hospital the visual acuities were 6/60 and counting fingers. Pupils were irregular, though responses were normal. No Ishihara plates were correctly identified, and examination of the visual fields showed reduced sensitivity, with patchy areas of loss indicative of retinal dysfunction. There were a few cells in both anterior chambers, intraocular pressures were normal, and there was considerable vitreous debris and syneresis. In the right eye there was a dense posterior vitreous infiltrate, with a limited posterior vitreous detachment. In the periphery large confluent areas of white retina extended almost 360°, with patchy pigmentation extending from the peripheral necrosis to the pre- and postequatorial regions (Fig 1). In the left eye there was a subtotal retinal



Figure 1 Retinal drawing of the right eye of case 1 showing peripheral retinal necrosis and scarring with early pigmentation.

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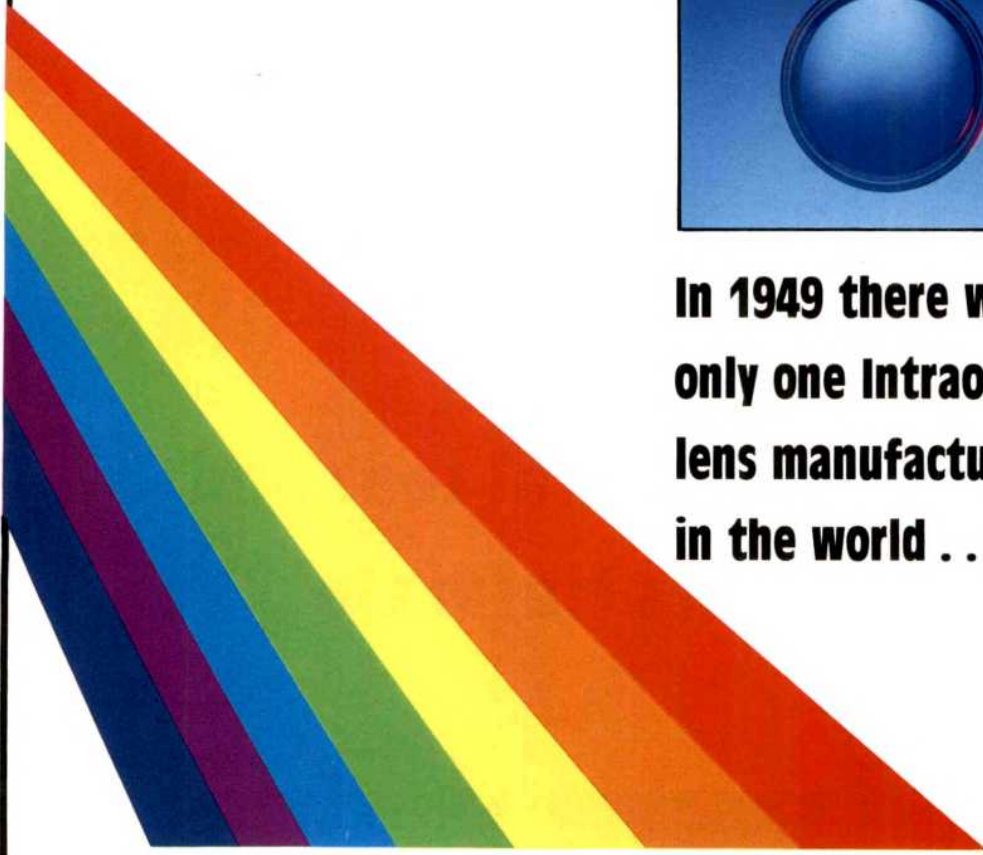
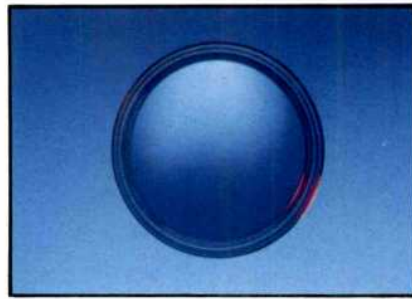
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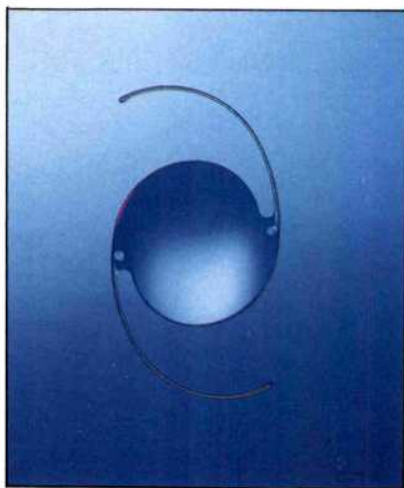
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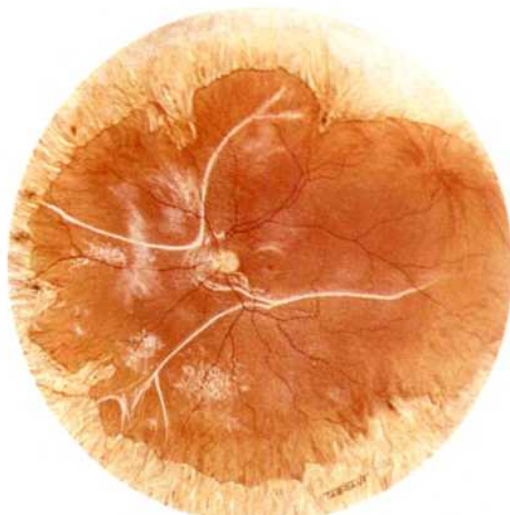


Figure 2 Retinal drawing of the left eye of a case 1 showing a subtotal retinal detachment with typical late phase peripheral retinal pigmentary changes characteristic of ARN.

detachment with no breaks apparent and several areas of subretinal fibrosis (Fig 2).

The blood picture was consistent with chronic disease with a low serum iron, though the haemoglobin was only slightly reduced. There was a relative lymphocytopenia of $0.61 \times 10^9/l$ (normal range $1.5-3.5$), and the total protein was 49 g/l (albumin 38 g/l , globulin 11 g/l ; normal range $20-35$). The hypogammaglobulinaemia was confirmed (in spite of the intravenous immunoglobulin treatment), with IgG 1.8 g/l (normal range $5.3-16.5$), IgA less than 0.1 g/l ($0.8-4.0$), and IgM less than 0.1 g/l ($0.5-2.0$). No antibodies to varicella zoster virus (VZV) or herpes simplex virus (HSV) were detected by complement fixation test (CFT) in serum or cerebrospinal fluid (CSF) taken in April 1988 following transfer to St Thomas's Hospital. Both were also negative for antibodies to toxoplasma by latex agglutination. VZV IgG was detected in serum but not CSF by enzyme-linked immunosorbent assay (ELISA), but VZV IgM was not detected in either specimen. Serological tests were unlikely to be helpful in this patient, since she had common variable hypogammaglobulinaemia and had received regular infusions of immunoglobulins. Furthermore, the samples for the tests were taken nine months after the onset of varicella, and at this stage one is unlikely to find evidence of a recent or current viral infection unless viral antigen persists in sufficient quantity.

The clinical appearances were consistent with late phase ARN. As treatment with acyclovir and local and systemic steroids had already been instituted with limited effect, no further medical treatment was undertaken. The common variable hypogammaglobulinaemia was treated with intravenous immunoglobulins (0.2 g/kg) to establish a serum IgG of 3 g/l .

In May 1988 left retinal detachment surgery was undertaken with cryopexy to necrotic retina, air injection, encirclement, and 30% SF₆ gas/air exchange. No retinal breaks were found at surgery. A vitreous aspirate was put into tissue culture, but no virus was isolated. Over the course of two weeks subretinal fluid was gradually reabsorbed, and, although subretinal

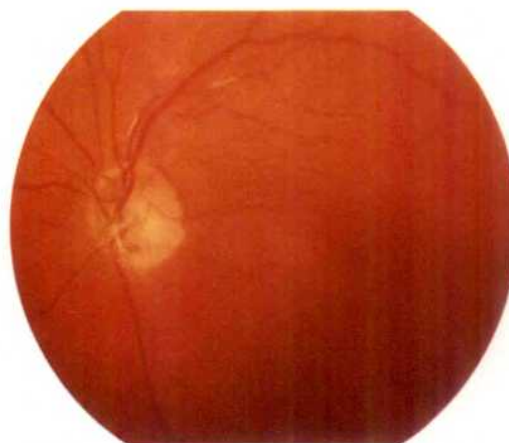


Figure 3A Colour photograph of case 2 taken at time of presentation showing an arteritis of the superior and inferior branch retinal arteries of the left eye.

fibrosis was still evident, the retina flattened. One year later vision in the right eye was $6/24$, and the left remained stable with counting fingers and good projection, with the retina attached.

CASE 2

Mrs V, a 61-year-old housewife, presented in February 1987 with a one-month history of blurred vision and floaters in the right eye. A diagnosis of mild acute anterior uveitis was made, which was treated topically. Unaided vision was RE $6/9$ and LE $6/12$. A few days later inflammatory cells were noted in the vitreous of the right eye and the diagnosis was revised to posterior uveitis. Shortly after this the vision in the right eye fell dramatically to counting fingers. She was otherwise entirely well, with no recent or previous medical history of note.

Examination of the right eye showed occlusion of peripheral and central retinal arterioles and a subtotal rhegmatogenous retinal detachment, with several small breaks at the junction between normal and necrotic retina. Peripheral arteritis was noted in the left eye as well as peripheral retinal necrosis (Figs 3A, B). A diagnosis of ARN was made based on the clinical appearances.

Routine haematological indices were entirely normal. A serum sample taken at the time of

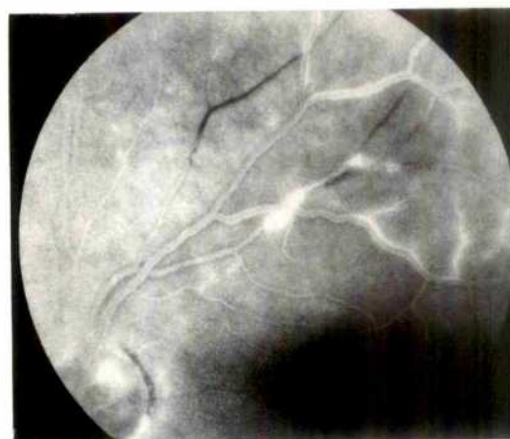


Figure 3B Fluorescein angiogram of the left eye of case 2 at presentation showing failure of the supero-temporal branch retinal artery with leakage from the vessel and secondary venous changes as well as optic disc hypo-fluorescence.

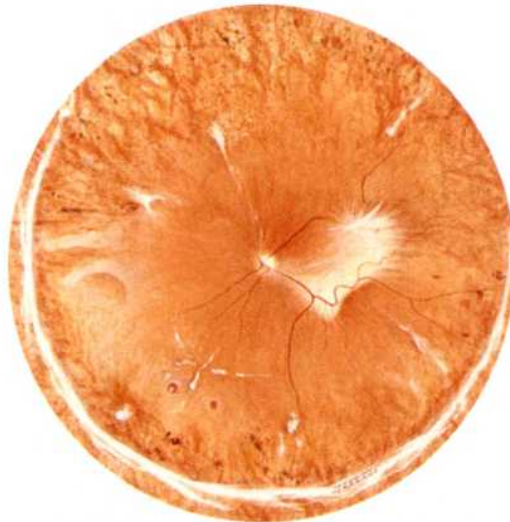


Figure 4 Retinal drawing of the left eye of case 3 showing a subtotal retinal detachment with periretinal fibrosis and retinal breaks in the inferonasal quadrant at junctions of normal and necrotic retina.

presentation had no detectable antibody to HSV or cytomegalovirus (CMV) but a titre of 20 to VZV by CFT. Two conventional retinal detachment procedures were undertaken before the right retina was successfully reattached. Vision improved to 6/18. The serum sample and a sample of subretinal fluid obtained at surgery were examined by ELISA for IgG antibodies to VZV and HSV and IgM antibodies to VZV. VZV IgG was twice as high in the subretinal fluid as in the serum. Furthermore, although VZV IgM was not detected in serum, it was detected at a high level in the subretinal fluid. These results were consistent with local antibody production, but one cannot be certain that they were not due to non-specific factors, since there are insufficient data on the serology of intraocular fluids. Unfortunately, there was insufficient subretinal fluid for tissue culture. The visual acuity in both eyes has remained stable (right 6/18 and left 6/12).

CASE 3

Mr K, a 40-year-old boat skipper, presented in November 1985 with decreased vision (6/60) in his left eye. On examination he was found to have a granulomatous panuveitis. His right eye was normal, and after treatment with systemic steroids (prednisolone enteric coated 20 mg once a day) the left eye improved to 6/24. A course of pulsed methylprednisolone (500 mg intravenously three times a day) improved visual acuity to 6/9, but one month later the panuveitis recurred, with signs of early involvement of the right eye. Treatment with systemic steroids (prednisolone enteric coated 20 mg once a day) was again instituted, and visual acuities stabilised at 6/5 and 6/18. He had previously been entirely well, and routine investigations to determine the cause of the uveitis gave normal results. In January 1986 he developed a shallow retinal detachment in the left eye and increased inflammation in the right despite further treatment with pulsed methylprednisolone.

On transfer to St Thomas's Hospital the vision in the right eye was 6/12 and in the left percep-

tion of light. There was a left relative afferent pupil defect. Colour vision (Ishihara plates) and visual fields in the right eye were normal. There were a few cells in the anterior chambers and in both vitreous cavities, with considerable syneresis in the left. There was a subtotal retinal detachment in the left eye with massive periretinal fibrosis and extensive peripheral chorioretinal scarring characteristic of late phase ARN (Fig 4). Several retinal breaks were detected at the junction of necrotic and normal retina. In the right eye similar typical late phase changes were present, with retinal folds and scarring superotemporal to the macula.

Routine haematological indices were normal. Other routine screening tests for uveitis, including serum angiotensin converting enzyme, gave normal results. Two serum samples were obtained in May and June 1986, with a left aqueous tap being performed at the same time as the second serum sample was taken. Antibodies to HSV were detected by CFT in both sera at a titre of 40 and in the aqueous at a titre of 8. Antibodies to VZV were also detected by CFT in both sera at a titre of 20 but at a titre of 32 in aqueous. Although this could be consistent with local production, leakage and concentration of antibody secondary to the vasculitic process found in this condition cannot be excluded. VZV and HSV IgG were detected in both sera and aqueous by ELISA, but VZV IgM was not detected in any of these samples. Aqueous was put into tissue culture but no virus was isolated.

Oral systemic steroids were continued in reducing doses. The appearances were consistent with late phase ARN, and it was thought that retinal detachment surgery for the left eye would not give any further visual improvement. Vision has remained unchanged since the patient's discharge in June 1986.

CASE 4

Mr L, aged 68, presented to the casualty department of St Thomas's Hospital in June 1984 with sudden onset of dizziness, nausea and vomiting, anorexia, difficulty in walking, and inability to concentrate. He was found to be pyrexial (39°C) and stuporose, with a blood pressure of 180/110 mmHg and a pulse of 100 beats per minute. There was some limitation of left gaze and evidence of left-sided sensory inattention. Plantar reflexes were upgoing.

On admission to hospital a lumbar puncture showed a lymphocyte pleocytosis ($75 \times 10^6/l$ white cells, 99% lymphocytes). A CT scan was normal. A presumptive diagnosis of herpes meningoencephalitis was made and treatment started with intravenous acyclovir (400 mg three times a day) and continued for three weeks. Antituberculosis triple therapy was also begun, as it was impossible to exclude this alternative diagnosis at the time of presentation. He had been entirely well beforehand. Apart from a mild leucocytosis the blood indices were within normal limits. Paired sera taken during the initial admission eight days apart showed a significant rise in antibodies by CFT to HSV (from <10–80). A significant rise in antibodies to HSV was subsequently shown in two CSF

samples taken at presentation in June and in August (from <4–32). Seroconversion was also demonstrated in the paired CSF samples by ELISA, and albumin/globulin ratios confirmed intrathecal synthesis of antibodies. These findings were consistent with the diagnosis of HSV meningoencephalitis. His condition improved slowly.

One month later, while still an inpatient, he developed a painful, red right eye with a panuveitis and reduced acuity (6/24). The left eye was entirely normal. Examination of the right fundus showed areas of peripheral confluent white retinitis, and a clinical diagnosis of HSV uveo-meningoencephalitis was made. Treatment with topical acyclovir (3% five times a day), dexamethasone (0.1% four times a day) and atropine (1% twice a day) was added to the regimen.

He was discharged on oral acyclovir (200 mg five times a day) combined with the topical regimen. Six weeks later he was readmitted complaining of decreased vision in the right eye, in which vision was found to have deteriorated to counting fingers. Further examination showed an extensive 360° peripheral retinal necrosis and a dense vitreous infiltrate.

Oral prednisolone 60 mg once a day was added, and the vision in the right eye improved slightly to 4/60. Once the eye was stable, the steroids were tailed off. In May 1987 a right cataract extraction was performed, with little improvement in acuity owing to macular oedema.

CASE 5

Mr G, aged 64, presented in September 1987 with a one-week history of a painful left eye and marked deterioration of vision. He had lost all useful vision in his right eye owing to uveitis in 1972. There had been no other relevant history of illness, and on admission he was entirely well. His right eye was phthisical and vision in the left was reduced to counting fingers. There was evidence of a left panuveitis with dense vitreous infiltrate and characteristic lesions of active ARN affecting the peripheral retina.

All haematological indices were within normal limits. Two serum samples were obtained one and two weeks after the onset of symptoms, and a CSF sample was also taken at presentation. There was no rise in antibodies by CFT to HSV, VZV, or CMV, and toxoplasma antibodies were not detected in either sample by latex agglutination. No antibodies were detected in the CSF by CFT. The first serum sample and the CSF were tested for VZV IgG and IgM by ELISA. VZV IgG was positive in the serum but not the CSF, and the test for VZV IgM was negative in both samples. These serological findings are consistent with immunity to varicella, and there was no evidence in support of a specific viral aetiology. Treatment was begun with acyclovir (350 mg intravenously three times a day) and systemic steroids (prednisolone enteric coated 50 mg once a day). After two weeks the retinal appearance improved, with reduction in the activity throughout the eye and improvement in vision to 3/60. Oral acyclovir 800 mg four times a day was then substituted for a further two weeks and the

steroids gradually tailed off. The optic disc was noted to be pale, the retinal vessels attenuated, and the peripheral retina necrotic, with areas of pigmentary scarring. He was discharged three weeks after admission and since then has had no further visual improvement.

CASE 6

Mrs D, aged 42, was referred for assessment after she had suffered a rapid deterioration of vision in her left eye in May 1988. The only previous ocular problem had been the onset of floaters in the left eye in December 1987, and there had been no pain or redness in either eye. Her general health was excellent.

On examination the visual acuities were right eye 6/5 and left eye 6/60. The anterior segments were normal. The left eye had a small vitreous haemorrhage and peripheral chorioretinal pigmentary scarring extending from 3 o'clock to 9 o'clock from the ora to the equator. The right eye was entirely normal.

The sudden deterioration in vision was due to the vitreous haemorrhage, and it seemed likely that the appearance of floaters five months earlier represented ARN which had resolved spontaneously, leaving the typical late phase appearances. Blood indices and results of virology studies proved to be normal. A serum sample taken in May 1988 provided no evidence to support any underlying causative agent, and since the clinical findings indicated no disease activity no active treatment was instituted. After two weeks the vitreous haemorrhage resolved, and subsequently the visual acuity improved to 6/6.

Discussion

Acute retinal necrosis (ARN; Kirasawa-type uveitis²⁴) was first described by Urayama *et al* in 1971.¹ In 1977 Willerson, *et al*²⁵ reported on two patients with bilateral necrotising vaso-occlusive retinitis of unknown origin. In 1978 Young and Bird described four cases of bilateral ARN. Since all previous cases had also been bilateral, the acronym BARN was adopted.²⁶ A viral aetiology was suspected but not proved. In 1980 Price and Schlaegel emphasised the severity of ARN by presenting the case of a 20-year-old girl who lost all useful vision within a few weeks.²⁷ Hayreh *et al* presented nine cases in 1980 of which only four were bilateral, and it was realised that the condition did not always affect both eyes.²⁸ Since these early descriptions about 60 cases have been reported in the world literature, and as 65% have been unilateral ARN has become the recognised description.

The stages of the disease process have been defined as acute and late. The syndrome has an insidious onset with a mild anterior uveitis and slight reduction in visual acuity. There may be ocular pain and increased intraocular pressure. A panuveitis follows. Rapid progression then ensues over a matter of days or weeks, during which time large areas of peripheral retina become white and necrotic, eventually coalescing to produce confluent peripheral retinal necrosis. A vaso-occlusive retinal vasculitis can

be observed during this phase, which particularly affects the retinal arterioles (Figs 3A, B). Vitreous turbidity is increased and retinal traction may begin at this stage.⁴ A swollen optic nerve head and arcuate neuroretinitis have been noted in the acute phase,²⁰ but most reports describe a relative sparing of the posterior pole. The second eye, if affected, usually becomes involved within weeks to months.

With evolution to the late phase the cloudy white, necrotic peripheral retinal areas regress, leaving sharply demarcated zones with mild pigmentary scarring (Fig 2) and increased vitreous debris.⁴ Visual acuity may rapidly worsen at this stage because of occlusion of vessels supplying the optic nerve head and central retina. Fibrous organisation of the vitreous may lead to traction retinal detachment. Rhegmatogenous detachment also occurs, the breaks usually being located at junctions between necrotic and normal retina (Fig 4). Surgery is technically difficult, and even with a good anatomical result (as in case 1) the final visual outcome may be poor because of optic atrophy, macular pucker, and macular oedema.^{3,4,22}

From 1982 onwards reports have implicated the herpes group of viruses in ARN.⁶⁻²¹ Culbertson *et al*⁶ examined an enucleated eye from a patient with ARN and confirmed histologically a retinal arteritis and eosinophilic intranuclear inclusions in the retinal cells consistent with herpes zoster retinitis.⁶ The sharp demarcation of affected retina was also confirmed histologically and is characteristic of cell to cell viral spread. Electron microscopy confirmed a herpes group virus, but specific serology was unhelpful. In 1986 Culbertson *et al*⁶ examined two more enucleated eyes from patients with ARN. Immunocytopathologic techniques confirmed the presence of VZV, which was also cultured from vitreous. Further confirmation was given by DNA restriction enzyme analysis. When these newer techniques were applied to material from the original case, VZV was detected.³

Numerous reports have supported the claim that ARN is caused by VZV.^{3,6-14} In 1986 Yeo

*et al*⁷ reported on two patients, one with the Ramsay-Hunt syndrome and the other with maxillary division shingles, both of whom developed ARN. Indirect immunofluorescence revealed VZV with evidence of recent varicella zoster infection in the serum. Jampol,⁸ Browning *et al*⁹ and Brown and Mendis¹⁰ described similar cases. Case 1 here provides further circumstantial evidence that VZV is a causative agent, since ARN developed only two weeks after chickenpox. So far as we are aware this is the first recorded instance of ARN developing in a patient with common variable hypogammaglobulinaemia.

ARN in immunocompromised patients is rare. Friberg and Jost¹³ reported on a patient who was immunosuppressed following renal transplantation and who developed ARN preceded by T2, T3, and T4 shingles with raised antibody titres to VZV. Similarly Freeman *et al*¹⁴ reported two cases of ARN in immunocompromised patients and one patient with AIDS. These cases have, however, been the exception. Cases 2 and 3 also support a VZV aetiology, since increased IgG and IgM to VZV was demonstrated in subretinal fluid (case 2) and high antibody titres to VZV in aqueous (case 3), both findings being suggestive of local antibody production.

Several other reports have implicated HSV as a causative agent.¹⁵⁻²¹ Peyman *et al* reported two cases responding to intravenous acyclovir.¹⁵ Viral cultures were negative, but vitreous aspirate stained positive for HSV with immunofluorescence techniques. Other cases of ARN have been described¹⁶ in which herpes simplex-like vesicles were simultaneously observed on the skin. Lewis *et al*¹⁷ have recently reported isolating HSV-1 virus from the vitreous of two patients with ARN. In one of these magnetic resonance imaging (MRI) suggested that virus had spread along both optic tracts from the lateral geniculate bodies. Interestingly, in earlier cases of presumed VZV ARN no similar spread could be detected, suggesting a possible distinction in activity between the two viruses. It would seem that, although HSV retinitis is similar to VZV ARN, the two are distinct entities. In 1976 Minckler *et al*¹⁸ reported the case of a 44-year-old man who died three weeks after simultaneous onset of HSV encephalitis and retinitis. The details are very similar to case 4 with the exception of the outcome, though the retinal changes described were not conclusively those of ARN. There was a 16-fold rise in HSV antibody within two weeks and cultures of brain tissue yielded HSV type 1. Intranuclear inclusion bodies typical of those produced by the herpes group were found in brain, optic nerves, retina, and choroid. Similarly, Cogan *et al*¹⁹ in 1964 described herpes simplex retinitis in a neonate, and a further description of HSV retinitis is given by Cibis *et al*.²⁰

Table 1 summarises the cases of ARN presented here. The herpes group of viruses was implicated in four of the six cases (Table 2). In cases 1, 2, and 3 (bilateral involvement) VZV was implicated, while in case 4 there was circumstantial evidence implicating HSV. In cases 5 and 6 the diagnosis was made on the typical fundus changes. Systemically these patients were

Table 1 Examination findings and retinal detachment descriptions in six cases of acute retinal necrosis

Case	Age	Sex	Examination findings	
			Right eye	Left eye
1	65	F	AC inflammation, vitreous infiltrate, confluent peripheral necrosis and pigmentation (Fig 1)	AC inflammation, subtotal traction, retinal detachment and peripheral pigmentary changes (Fig 2)
2	61	F	AC inflammation, vitreous inflammation, retinal arteritis and subtotal rhegmatogenous detachment. Retinal breaks at demarcation lines	Peripheral retinal arteritis and peripheral retinal necrosis (Figs 3A, B)
3	40	M	Mild panuveitis with increased activity later and peripheral areas of confluent pigmentation and scarring	Mild panuveitis leading to a marked panuveitis and shallow subtotal RD with numerous breaks and massive periretinal fibrosis and peripheral scarring (Fig 4)
4	68	M	Dense vitreous infiltrate with extensive peripheral retinal necrosis. Macula oedema developed	Normal
5	64	M	Phthisical (uveitis 1972 no details)	Panuveitis and dense vitreous infiltrate. Typical acute retinal necrosis changes with peripheral pigmentary changes and optic atrophy
6	42	F	Normal	Confluent peripheral retinal scarring, vitreous haemorrhage and debris from recent posterior vitreous detachment

AC=anterior chamber, RD=retinal detachment.

Table 2 Final outcome and supporting evidence pointing to a herpes group virus as the aetiological agent

Case	Final visual acuity		Follow-up period	Evidence for proposed aetiology
	Right	Left		
1	6/24	CF	1 year	Varicella zoster rash two weeks prior to the onset of typical acute retinal necrosis
2	6/18	6/12	1 year	Systemically well. VZV IgM detected in subretinal fluid but not in the serum and a relatively high VZV IgG titre in the subretinal fluid compared with serum
3	6/12	PL	2 years	Systemically well. A higher VZV complement fixation titre in aqueous than in serum (both samples taken at the same time)
4	4/60	6/6	1 year	Serologically confirmed HSV uveo-meningoencephalitis followed by ARN one month later
5	NPL	3/60	18 months	No systemic associations and no serological evidence in support of a viral aetiology
6	6/5	6/6	1 month	No systemic association. Negative serology

CF=counting fingers. (N) PL=(no) perception of light.

normal and there was no justification for taking intraocular specimens. Three of the six cases were unilateral (though it is not possible to be sure of the nature of the previous 'uveitis' in the right eye of case 5).

Table 2 summarises the visual outcome. It is noteworthy that the cases with bilateral involvement (1, 2, and 3) had a poorer prognosis because of retinal detachment. In case 2, however, a relatively good result was achieved in the right eye following detachment surgery. Case 4 (right eye affected) did poorly because of macular oedema rather than retinal detachment, and case 5 (left eye) had a final visual acuity of 3/60 18 months later because of optic atrophy. Matsuo *et al* reported a mild case of ARN,²³ and it would seem that from our experience over the past four years a spectrum of ARN exists from mild uniocular disease, as in case 6, to severe blinding bilateral disease.

The rarity of the disease makes a definitive approach to its management difficult. The diagnosis is essentially clinical, being suggested by retinal arteritis (which is an uncommon feature in uveitis in contrast to phlebitis) and the pathognomonic peripheral confluent retinal infiltration. The diagnosis should be supported by evidence of systemic infection, though this will be negative in most cases, and the appropriate analysis of intraocular specimens where these can be obtained. In the early stages intravenous acyclovir limits the retinal necrosis, and steroids reduce the ocular inflammation, though to what extent these improve the natural history of the condition is still unknown, as some cases, for example, case 6 and that of Matsuo *et al*,²³ had a relatively benign and self limited course. Antiplatelet drugs have been given to some patients with the object of limiting the occlusive vasculitis, but this is an unproved treatment.

Retinal detachment occurred in three eyes. The causes were rhegmatogenous in two and traction in the third. In contrast to the other series no large breaks or giant tears were found. Han *et al*²² reported the effects of prophylactic laser photocoagulation to prevent detachment from retinal breaks at areas of demarcation between necrotic and normal retina in five patients. After 15 months of follow-up no retinal detachments had occurred. These patients were also treated concurrently with acyclovir, steroids,

and antiplatelet agents, all of which may have influenced the outcome.

The possibility of ARN in any patient presenting with an anterior uveitis and particularly in those with a recent history of herpes simplex or zoster infections must always be considered. Thorough examination of the peripheral fundus should be carried out in all cases to look for the physical signs of ARN, so that early diagnosis may be achieved, followed by appropriate chemotherapy and monitoring.

We thank Mr M D Sanders for allowing us to report case 4.

- 1 Urayama A, Yamada N, Sasaki T, *et al*. Unilateral acute uveitis with retinal peri-arteritis and detachment. *Jpn J Clin Ophthalmol* 1971; 25: 607-19.
- 2 Culbertson WW, Blumenkranz MS, Haines H, Gass DM, Mitchell KB, Norton EWD. The acute retinal necrosis syndrome. Part 2. Histopathology and aetiology. *Ophthalmology* 1982; 89: 1317-25.
- 3 Culbertson WW, Blumenkranz MS, Pepose JS, Stewart JA, Curtin VT. Varicella zoster virus is a cause of acute retinal necrosis syndrome. *Ophthalmology* 1986; 93: 559-69.
- 4 Fisher JP, Lewis ML, Blumenkranz MS, *et al*. The acute retinal necrosis syndrome. Part 1. Clinical manifestations. *Ophthalmology* 1982; 89: 1306-16.
- 5 Clarkson JG, Blumenkranz MS, Culbertson WW, *et al*. Retinal detachment following the acute retinal necrosis syndrome. *Ophthalmology* 1984; 91: 1665-8.
- 6 Schwartz JN, Cashwell F, Hawkins HK, *et al*. Necrotising retinopathy with herpes zoster ophthalmicus. A light and EM study. *Arch Pathol Lab Med* 1976; 100: 386-91.
- 7 Yeo JH, Pepose JS, Stewart JA, Sternberg P, Liss RA. Acute retinal necrosis syndrome following herpes zoster dermatitis. *Ophthalmology* 1986; 93: 1418-22.
- 8 Jampol LM. Acute retinal necrosis. *Am J Ophthalmol* 1982; 93: 254-5.
- 9 Browning DJ, Blumenkranz MS, Culbertson WW. Association of varicella zoster dermatitis with acute retinal necrosis. *Ophthalmology* 1987; 94: 602-6.
- 10 Brown RM, Mendis U. Retinal arteritis complicating herpes zoster ophthalmicus. *Br J Ophthalmol* 1973; 57: 344-6.
- 11 Soudi S, Ozawa H, Matsushashi M, Shimazaki J, Saga U, Kurata T. Demonstration of varicella zoster viral antigens in the vitreous aspirates of patients with acute retinal necrosis syndrome. *Ophthalmology* 1988; 95: 1394-8.
- 12 Imura N, Imura R, Oku H, *et al*. Rise of antibody titre for varicella zoster virus in the aqueous and vitreous in two cases with Kurasawa uveitis. *Jpn J Clin Ophthalmol* 1985; 39: 101-6.
- 13 Friberg TR, Jost BF. Acute retinal necrosis in an immunocompromised patient. *Am J Ophthalmol* 1984; 98: 515-7.
- 14 Freeman WR, Thomas EL, Rao NA, *et al*. Demonstration of herpes group virus in acute retinal necrosis syndrome. *Am J Ophthalmol* 1986; 102: 701-2.
- 15 Peyman GA, Goldberg MF, Uninsky E, Tessler H, Pulido J, Hendricks R. Vitrectomy and intravitreal drug therapy in acute retinal necrosis syndrome. *Arch Ophthalmol* 1984; 91: 1659-64.
- 16 Ludwig IH, Zegarra H, Zakov ZN. The acute retinal necrosis syndrome; possible herpes simplex retinitis. *Ophthalmology* 1984; 91: 1659-64.
- 17 Lewis ML, Culbertson WW, Post JD, *et al*. Herpes simplex virus type 1. A cause of the acute retinal necrosis syndrome. *Ophthalmology* 1989; 96: 875-8.
- 18 Minckler DS, McLean EB, Shaw CM, Hendrickson A. Herpes hominis encephalitis and retinitis. *Arch Ophthalmol* 1976; 94: 89-95.
- 19 Cogan DG, Kuwabara T, Young GF, *et al*. Herpes simplex retinopathy in an infant. *Arch Ophthalmol* 1964; 72: 641-5.
- 20 Cibis GW, Flynn JT, Davis AB. Herpes simplex retinitis. *Arch Ophthalmol* 1978; 96: 299-302.
- 21 Sarkies N, Gregor Z, Forsey T, Darougar S. Antibodies to herpes simplex type 1 in intraocular fluids of patients with acute retinal necrosis. *Br J Ophthalmol* 1986; 70: 81-4.
- 22 Han DP, Lewis H, Williams GA, Mieler WF, Abrams GW, Aaberg TM. Laser photocoagulation in the acute retinal necrosis syndrome. *Arch Ophthalmol* 1987; 105: 1051-4.
- 23 Matsuo T, Nakayama T, Koyama T, Koyama M, Matsuo N. A proposed mild type of acute retinal necrosis syndrome. *Am J Ophthalmol* 1988; 105: 579-83.
- 24 Bando K, Kinoshita A, Mimmura Y. Six cases of so-called Kurasawa-type uveitis. *Jpn J Clin Ophthalmol* 1979; 33: 1515-21.
- 25 Willerson D, Aaberg TM, Reeser FH. Necrotising vaso-occlusive retinitis. *Am J Ophthalmol* 1977; 84: 209-19.
- 26 Young NJA, Bird AC. Bilateral acute retinal necrosis. *Br J Ophthalmol* 1978; 62: 581-90.
- 27 Price FW, Schlaegel TF. Bilateral acute retinal necrosis. *Am J Ophthalmol* 1980; 89: 419-24.
- 28 Hayreh MMS, Krieger AE, Straatsma BR, *et al*. Acute retinal necrosis. *Invest Ophthalmol Vis Sci* 1980; 19 (suppl 48): ARVO abstracts.
- 29 Margolis T, Irvine AR, Hoyt WF, Hyman R. Acute retinal necrosis syndrome presenting with papillitis and arcuate neuroretinitis. *Ophthalmology* 1988; 95: 937-40.

Capillary haemangiomas: an approach to their management

M J Boyd, J R O Collin

Abstract

Twenty-five children with eyelid haemangiomas were reviewed. Fifteen patients with enlarging lesions thought to be at risk of causing amblyopia were treated with intralesional steroids as soon after presentation as possible. This appeared to reduce significantly the incidence of amblyopia. Surgery was reserved for older children in whom no further involution of the lesion was expected.

Capillary haemangiomas of the lid are a distinct clinical entity in children. They threaten vision by causing anisometropia, sensory deprivation, amblyopia, and strabismus.¹ Their management and its effectiveness have remained controversial owing to the high complication rate and uncertain success of any treatment. The tumours follow a characteristic clinical course, appearing shortly after birth, growing quickly in the first year of life, and then beginning a slow, involutional phase; 40% resolve by age 4 and 70% by age 7.² Despite this the risk of amblyopia has encouraged a variety of treatments to be used. Radiotherapy is associated with cataracts and cutaneous scarring, and sclerosing agents with scarring and unpredictability. Radon seeds and cryotherapy both cause cutaneous atrophy. Eventually intralesional steroids were tried, first as an addendum to a trial of systemic steroids by Zarem and Edgerton,³ then more extensively by Mazzola⁴ and Kushner.⁵

For 10 years we have been using intralesional steroids during the active phase of lesional growth and with adjunctive treatment (occlusion and glasses). Surgical debulking is done if necessary at a later inactive phase. We present our results on 25 patients over a 10-year-period.

Subjects and methods

All the patients had capillary haemangiomas diagnosed by virtue of the history of onset and progression of disease and the appearance of the lesions. Seventeen of the 25 patients were female (68%). Sixteen (64%) were symptomatic within two weeks of birth and 23 (92%) before three months. The patients presented to our clinic between the ages of 1 month and 7 years. Twenty of 25 patients' lesions (80%) were on the upper lid. The largest and smallest axes of the lesions were measured, but computerised tomography was not routinely performed, and without this it was impossible to assess the variable bulk and volume of the lesions.

Treatment was thought to be warranted if the lesion threatened the visual axis or if there were signs suggesting amblyopia (strabismus or refractive error). In accordance with their

severity some lesions were followed up expectantly; the children were refracted and treated with glasses and occlusion therapy as necessary. Other children, in whom amblyopia was a greater risk, received steroid injections. The routine injection consisted of 40 mg of methylprednisolone and 4 mg of dexamethasone sodium phosphate. The first was injected directly into the lesion, and the second, more soluble, was injected perilesionally. The direct intralesional injection was given deeply to prevent long-acting depotsteroid deposits from being visible under the skin. The perilesional injection was given subcutaneously round the periphery of the haemangioma. The injections were repeated three times at approximately six-week intervals if there was some response but no gross decrease in the size of the lesion. Two patients had a total of four injections each.

Surgery consisted of lid debulking or adjusting lid height or contour and was done only after the tumour had passed into an inactive growth phase, usually after the age of six. Twenty two patients presented to us without any previous treatment, but three had initially undergone treatment elsewhere: one had a course of cryotherapy followed by one course of steroid injection; one had had two courses of cryotherapy; and one arrived with ptosis after surgical excision.

Results

Of the 25 patients 15 needed occlusion treatment, nine required glasses, and 15 had intralesional steroids. Of those not treated with steroids six had presented prior to its usage, two were children with lesions not warranting injections (too small or thought not to be at risk of causing amblyopia) and two presented after the active growth phase of the tumour had ended.

Twelve of the 15 (80%) required only one or two injections, but one case needed three and another two needed four. The injections often initially caused some extravasation of blood. The patients were reviewed after four weeks when any haematoma had absorbed. A subjective assessment was made by asking the parents if they thought the lesion had regressed, and an objective assessment was made by measuring the major and minor axes of the lesion. The injections had a significant reducing effect in nine of 15 (60%) cases (Figs 1A, B), questionable effect in four, and little or no effect in two (Figs 2). In those cases that responded there was a considerable reduction in subcutaneous vascularity as well as a reduction in bulk, but this was not easy to quantify. If subjectively and objectively there was a dramatic response, the injection was not repeated, but if there was only a partial improve-



Figure 1A Four-month-old child with actively enlarging upper lid haemangioma.



Figure 1B Same child three months after steroid injection showing rapid resolution.

ment the injection was repeated up to four times. If there was no response or the lesion actually increased in size despite the injection, it was not repeated. It was not possible to identify the factors which made it more likely that some lesions would respond while others would not. No systemic side effects from the steroids were noted. Follow-up for all patients was a mean of 1 year 11 months, being more than twice as long for the non-injected group – 1 year 4 months (range 3 months to 3 years) versus 2 years 10 months (range 1½ to 5 years).

The main reason for treating the patients, particularly with steroids, was the risk of amblyopia. Amblyopia is described as a unilateral or bilateral decrease in vision for which no obvious cause can be detected.⁶ It proved to be a major complication with these tumours, occurring in 64% of our cases (16/25). It occurred in eight out of 10 cases (80%) treated without steroids and in eight of 15 (53%) receiving steroid injections. It was much more frequent with the upper lid lesions, being seen in 16 of 20 cases (80%) compared with 1 of 5 (20%) patients with lower lid lesions. This single case of lower lid haemangioma was associated with long-term dense amblyopia and was left with counting finger vision in the affected eye, but the lesion was very large (Fig 3). Although it was not possible to measure the lesions accurately, it was noted that, if the lesion was near the eyelid margin and the visual axis was threatened or occluded, amblyopia was common. We did not find that earlier injections gave better visual results than the later ones. The most amblyopic cases in the injected groups included both a child who had been injected at the earliest age (2 months) with an end vision of hand movements and the child who had been injected at the latest

age (2½ years) with an end vision of counting fingers.

Six children had a total of eight operations at a mean age of 7½ years to correct the residual bulk of the lesion, entropion, ectropion, or ptosis. Five operations were debulking procedures via an anterior skin approach (with one including an anterior lid repositioning); one was a full-thickness lid resection (Fig 4), another was a ptosis repair (anterior levator resection), and the remaining operation was a skin crease reformation procedure. Postoperatively the results were satisfactory, though in two cases the skin crease was not exactly symmetrical and the ptosis was slightly overcorrected in one case and undercorrected in another.

Discussion

There have been several large studies reviewing either the complications or treatment of capillary haemangiomas of the lid. Stigmar *et al*⁷ reviewed 51 cases of eyelid haemangiomas and found 27 with ophthalmic complications: 44% developed amblyopia and 34% strabismus. They advocated a close follow-up with surgery, steroids, or x rays if vision was threatened. Cosmetic repair was delayed until age 8.

Haik *et al*¹ analysed their results of treating 101 eyelid haemangiomas. Clinical features included early recognition by the family (95% by 6 months of age) and female predominance (61%) and superior lid involvement (75%). Forty eight cases had long-term follow-up, with 60% showing amblyopia, usually secondary to sensory deprivation or anisometropia. Various types of treatment were used, but the type of treatment did not noticeably alter the cosmetic or functional outcome. Kushner⁸ was an early advocate



Figure 2A Three-month-old child with actively enlarging upper lid haemangioma.



Figure 2B Same child one year after steroid injections showing progression of lesion despite treatment.



Figure 3 Two-year-old child with large lower lid haemangioma causing amblyopia.



Figure 4A Seven-year-old child with involuted upper lid haemangioma.

of intralesional steroids and has reported his results of injecting 25 eyelid haemangiomas. Total resolution occurred in 16; seven showed less than 50% decrease in the size of the lesion, but enough resolution to prevent amblyopia. Only three cases failed to respond to treatment.

Our study confirms many of these findings. They include the high female predominance, predilection for the upper lid, and early clinical presentation. Amblyopia remains the foremost complication, occurring in 64% of the cases in our study. Its frequency emphasises the need for early treatment and early follow-up. There was a reduction in the frequency of amblyopia with the use of injectable steroids (80% down to 53%), and this should become more pronounced as the follow-up becomes longer.

We elected to use the same dosage of intra- and perilesional steroids for all haemangiomas as described by Kushner.^{5,8} Bonavolonta *et al*⁹ adjusted the injectable steroid dose to the size of the haemangioma as determined by CT, but they could not prove that this method was more successful, and at least one case developed Cushing's syndrome. Our arbitrary approach with a common steroid dose irrespective of size or location of the tumour showed a successful method of managing this lesion without major complications.

Surgery in this study was limited to the inactive growth phase of the tumour. It was used in cosmetic debulking procedures and was routinely successful. It was not associated with excessing haemorrhage or rebound growth. Technically the skin crease and lid height were most difficult to predict postoperatively.

In conclusion, eyelid haemangioma remains a distinct clinical entity associated with a high risk of amblyopia and complications from treatment. A method of management has been described which includes an intralesional steroid injection in sight threatening lesions, with elective



Figure 4B Same child after debulking and full-thickness lid resection of the upper lid haemangioma.

surgical debulking at a later age. This treatment is successful in diminishing tumour size and the risk of amblyopia and is associated with minimal complications.

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- Haik GR, Jakobiak FA, Ellsworth RM, Jones IS. Capillary Hemangioma of the lids and orbit: an analysis of the clinical features and therapeutic results in 101 cases. *Ophthalmology* 1979; **86**: 760-89.
- Margileth A, Museles M. Cutaneous Hemangioma in children: diagnosis and conservative management. *J Am Med Assoc* 1965; **194**: 523-6.
- Zarem HA, Edgerton MT. Induced resolution of cavernous Hemangiomas following prednisolone treatment. *Plast Reconstr Surg* 1967; **39**: 76-83.
- Mazzola RF. Treatment of haemangiomas in children by intralesional injection of steroids. *Chirurg Plast (Berlin)* 1978; **4**: 161-71.
- Kushner BJ. Intralesional corticosteroid injection for infantile adnexal Hemangioma. *Am J Ophthalmol* 1982; **93**: 496-506.
- Von Noorden GK. Binocular vision in ocular motility. St Louis: Mosby, 1980: 219.
- Stigmar G, Crawford JS, Ward, CM, Thompson HG. Ophthalmic sequelae of infantile hemangiomas of the eyelids and orbit. *Am J Ophthalmol* 1978; **85**: 806-13.
- Kushner BJ. Capillary haemangiomas of the adnexa in infants. *Oculoplastic orbital and reconstructive surgery I: Eyelids*. Hornblass A, eds. In: Baltimore: Williams and Wilkins, 1988: 243-50.
- Bonavolonta G, Vassallo P, Uccello G, Tranfa F. Our experience with intralesional corticosteroid injection therapy for infantile adnexal hemangioma. *Orbit* 1985; **4**: 177-81.



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Normalisation of refractive error after steroid injection for adnexal haemangiomas

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Abstract

A longitudinal study of 27 patients with infantile haemangiomas is reported. It confirmed the efficacy of local steroid injection as a method of treatment; 81.5% of patients showed a marked improvement, with the lesion reducing to 25% or less of its original size. Involution was most marked in the first two weeks but continued for up to four months after injection. Amblyopia was present in 43% of children and was usually the result of induced refractive error rather than obstruction of the visual axis or strabismus. Anisometropia was found in 68% of children, with a high incidence of asymmetric astigmatism on the side of the haemangioma. Following local steroid injection a marked reduction in astigmatism was noted in 53.8% of children, a lesser reduction in 15.4%, and no reduction in 30.8%. Successful treatment of the haemangioma, therefore, may not remove the risk of amblyopia, and regular refraction and visual assessment remain mandatory.

Infantile haemangiomas affect between 3%¹ and 8%² of the population. They have a predilection for the face and commonly appear within the first two months of life. There is a phase of rapid enlargement over the first four to eight months, followed by a period of stability and subsequent spontaneous involution, with 70% having regressed by seven years of age.³

In addition to the cosmetic blemish 43-60% of children with adnexal haemangiomas will develop strabismic, anisometropic, or deprivation amblyopia. A smaller number will develop other ocular complications including exophthalmos, exposure keratitis, or optic atrophy.^{4,5} Previous studies in this unit have shown that the majority of cases of amblyopia result from anisometropia rather than strabismus or occlusion of the visual axis.⁶ Robb⁷ also found a 46% incidence of asymmetric refractive error in affected children.

Several methods of treatment (including surgical excision, cryotherapy, irradiation, and injection of sclerosing agents) have been used for infantile haemangiomas, but all have a risk of local or systemic complications.⁸ Similarly, though effective, systemic steroids may adversely affect the child's growth, and therefore intralesional steroid injections were introduced in the late 1970s. These have been shown to promote rapid resolution of the haemangioma,^{9,12} but the natural history of the refractive error following treatment has not been explored (though Kushner¹¹ noted reversal of refractive error in one child following early treatment).

Since December 1981 we have treated 27

children with adnexal haemangiomas by means of local steroids. We report the results of treatment in this group with respect to resolution of the lesion, the effect on refractive error, and the long term visual outcome.

Patients and methods

The diagnosis of haemangioma was based on the clinical appearance of either a raised, red, dimpled lesion involving the superficial skin, or a 'subcutaneous' swelling or fullness with a dark reddish blue discolouration, together with a history of onset, growth, and tendency of the lesion to increase in size when the patient cried.

All children were examined for evidence of haemangiomas in other sites, and a CT scan was performed to define the limits of the adnexal haemangioma where extension into the orbit was suspected. Two patients required biopsy to establish the diagnosis because of clinical suspicion of an underlying rhabdomyosarcoma.

The haemangiomas were measured and photographed immediately before injection and at least once after injection. The size was noted and the position recorded by the same notation as employed in spectacle trial frames. For example, a lesion extending from the 60° axis to the 150° axis was considered to have a 90° extent. Cycloplegic refraction (by streak retinoscopy after the instillation of cyclopentolate 1%) and fundal examination were performed prior to injection in 25 of the children, the remaining two having haemangiomas remote from the eyelids. Refraction and fundal examination were repeated at intervals after injection.

Indications for treatment of adnexal haemangiomas were as Kushner¹³ advised: occlusion of the visual axis, strabismus, an asymmetric refractive error sufficient to cause amblyopia, or the tumour enlarging and showing the potential for the above problems. Intralesion injections of steroids were undertaken under general anaesthetic, a combination of triamcinolone (20-40 mg) and dexamethasone (4 mg) being given. In one early case methylprednisolone (40 mg) was used in place of dexamethasone. In the first five cases the steroid was injected round the margins of the lesion; thereafter injections were

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Table 1 Degree of resolution of haemangioma following local steroid injection

Grade of response	No. of patients
0	2
1	2
2	1
3	10
4	12
Total	27

Table 2 Ophthalmic sequelae in children with an adnexal haemangioma and amblyopia

Complication	No. of patients
Asymmetric astigmatic error >0.75 D	7
Asymmetric astigmatic error + strabismus	1
Asymmetric astigmatic error + lid occlusion	1
Asymmetric anisometropia + hypermetropia	1

given directly into the lesion at multiple sites to minimise the possibility of subcutaneous fat atrophy following treatment. Care was taken to avoid direct injection into the vascular channels. If resolution of the haemangioma was incomplete, a further injection was carried out between six weeks and eight months after the first.

The response to treatment was graded from 0 to 4:

0	representing	<25%	resolution
1	representing	≥25% <50%	resolution
2	representing	≥50% <75%	resolution
3	representing	≥75% <100%	resolution
4	representing	100%	resolution

Where possible monocular visual acuities were obtained before injection and at subsequent post-injection visits. Methods appropriate for age were used, including the acuity card procedure¹⁴ in some infants.

Results

Of the 27 children treated 19 were female and eight male. Fifteen lesions involved the upper lid, eight the lower lid, and two both the upper and lower lids. One haemangioma was located over the left parotid gland and one on the upper lip.

The age at treatment ranged from 3 months to 34 months (mean 10.6 months), with the exception of one patient who was treated at 14 years of age. Twenty patients were under the age of 12 months at the time of first injection. Follow-up ranged from six months to 73 months (mean 24.1 months). One child showed a grade 2 response two weeks after injection, but died of a streptococcal pneumonia three weeks after injection; there was no evidence at the time of any systemic effect of the steroids on this child and in particular no evidence of immune suppression.

Sixteen of the 27 patients received a second injection because of incomplete resolution of the haemangioma, the time interval between injections ranging from six weeks to eight months. Two patients received a third injection before achieving satisfactory resolution, and one patient received four injections but showed a grade 0 response. Involution was most marked in the first two weeks and continued for up to four months after injection.

RESOLUTION OF HAEMANGIOMA

Table 1 summarises the response of the patients to injection. Twenty two patients showed a grade 3 or 4 response, three patients showed a grade 1 or 2 response, and two patients showed a grade 0 response. Of the children showing no response to treatment one was aged 3 months and the other 14 years at the time of first injection.

Table 3 Asymmetric astigmatism related to the site of the haemangioma

Site of haemangioma	No. patients with asymmetric astigmatism	No. patients without asymmetric astigmatism
Upper lid	12	2
Lower lid	1	5
Combined upper + lower lid	2	0

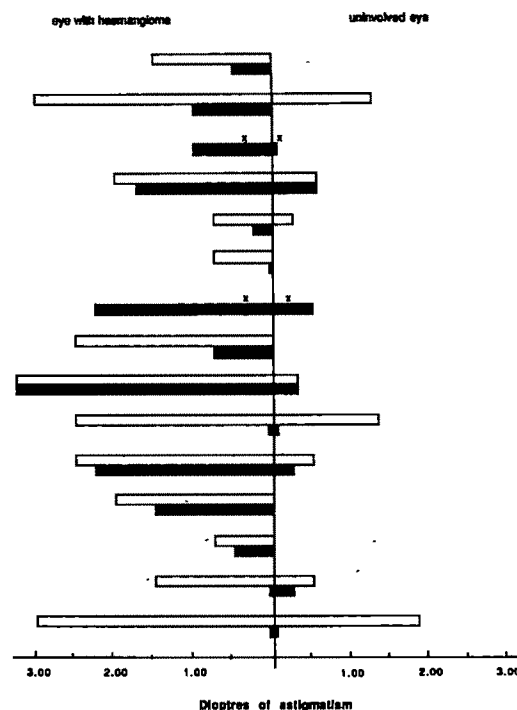


Figure 1 Astigmatic errors in children with infantile haemangiomas. Each pair of bars represents the astigmatism of one eye of each patient. White bars: preinjection. Black bars: postinjection. X = data unavailable.

Following injection one child developed an area of subcutaneous fat atrophy which resolved over a period of six months. This child was one of the first five to receive treatment, and steroid had been injected round the margins of the lesion. To minimise the possibility of this complication subsequent injections were given directly into the haemangioma at multiple sites, with no evidence of subcutaneous fat atrophy in the following 22 children.

A second girl developed an abscess at the site of injection, though this occurred three weeks after injection and followed a direct blow to the lid. One child showed an unusual response with apparent complete resolution of the haemangioma within four weeks of injection, but with recurrence of the lesion which then remained at one-quarter of its original size despite two further injections.

VISUAL OUTCOME

Two of the 27 patients were treated for non-sight threatening lesions and two were lost to follow-up before accurate monocular acuities were obtained. Of the remaining 23 patients 10 (43%) developed amblyopia, all on the side of the haemangioma, with amblyopia defined as two or more lines of Snellen acuity less than the preferred eye. With the exception of one child who presented at the age of 14 years these children are still receiving amblyopia therapy.

By Jampolsky's criteria for significant anisometropia¹⁵ all 10 children had significant asymmetric refractive error (Table 2). Seven had astigmatism alone, one astigmatism and strabismus, one astigmatism combined with lid closure, and one anisohypermetropia.

Of the 25 patients with lid involvement refractive data were not available for one child

Table 4 Astigmatism associated with adnexal haemangiomas

Case	Position of the haemangioma in relation to the limbus (degrees)	Initial size of haemangioma, height × width (cm)	Refractive error of involved eye before injection	Final refractive error of involved eye after injection	Age at first injection (months)	Number of injections received	Length of follow-up (months)	Ophthalmic sequelae
1	90–150	2.5 × 3.25	−1.00/+3.00 × 110	+1.50 sph	6	2	6	Amblyopia
2	240–90	4.50 × 4.75	+3.50/+1.50 × 155	+2.00 sph	15	2	46	Normal vision
3	80–180	3.25 × 1.5	−0.25/+0.75 × 180	−0.75/+0.50 × 180	3	1	18	Amblyopia
4	305–360	2.5 × 2.25	−0.50/+2.00 × 180	0.00/+1.50 × 180	3	2	12	Normal vision
5	90–150	3.0 × 2.0	−2.00/+2.50 × 120	−0.75/+2.25 × 120	12	2	21	Amblyopia
6	90–180	2.5 × 2.5	+1.50/+2.50 × 125	+0.75 sph	5	2	24	Normal vision
7	50–160	3.25 × 2.0	−2.00/+3.25 × 120	−2.00/+3.25 × 117	14 yr	3	31	Amblyopia
8	0–180	3.5 × 3.0	+1.50/+2.50 × 125	+1.25/+0.75 × 175	5	2	10	Normal vision
9	25–130	4.75 × 3.25	*	+0.25/+2.25 × 90	6	1	29	Amblyopia + lid occlusion
10	20–90	2.25 × 2.0	+0.50/+0.75 × 120	+0.75 sph	6	1	13	Normal vision
11	320–240	7.25 × 6.5	+0.25/+0.75 × 80	+0.00/+0.25 × 80	6	2	10	Amblyopia
12	80–140	2.0 × 1.25	+5.00/+2.00 × 90	+2.75/+1.75 × 95	16	1	19	Amblyopia + strabismus
13	315–35	3.75 × 2.75	*	+1.50/+1.00 × 180	3	4	67	Amblyopia
14	20–160	3.0 × 1.25	+1.50/+3.00 × 90	+2.00/+1.00 × 90	5	2	6	Amblyopia
15	80–120	2.5 × 1.5	+0.50/+1.50 × 90	+0.50/+0.50 × 90	6	1	13	Normal vision

*Data unavailable.

with an upper lid lesion and two children with a lower lid lesion. Of the remainder 15 (68%) had significant astigmatism (Fig 1) with only two children with upper lid involvement and five children with lower lid involvement showing no astigmatic error on the side of the haemangioma (Table 3).

In all 15 patients with astigmatism the axis of the plus cylinder was found to be perpendicular to the main axis of the haemangioma (Table 4). Table 4 also indicates the change in astigmatism between the preinjection and postinjection refractions for the 13 children with complete refractive data. In seven of the 13 children (53.8%) astigmatism was either eliminated or greatly reduced (by 1.50 dioptres or more). In two children (15.4%) astigmatism was reduced by 0.50 dioptre, but in four children (30.8%) astigmatism remained unchanged despite the fact that three showed a good response to treatment in the first 18 months of life. Three children showed a reduction in astigmatism in the uninvolved eye of 1.50 (two) or 2.00 dioptres (Fig 1).

The spherical equivalents of refractive error for 22 patients prior to treatment are presented in Figure 2. Three patients were found to be myopic on the side of the haemangioma and two on the uninvolved side. Only one patient with myopia was noted to have amblyopia and he was also found to have an asymmetric astigmatic error of +2.50 dioptres cylinder on the side of the haemangioma. This patient had a reduction of myopia following treatment from −0.75 dioptre to +0.25 dioptre. One further patient, who was not amblyopic, had a reduction of myopia from −1.25 dioptres to −0.50 dioptre following steroid injection. The third patient was unchanged at −0.75 dioptre.

Discussion

This study confirms that local injections of steroids are a simple method of achieving a high rate of resolution of adnexal haemangiomas. 81.5% of patients (22 of 27) showed a marked response, the lesion reducing to 25% or less of its original size. Only two patients showed no response, and this included one girl who was 14 years old at the time of first injection.

The mechanism of action of local steroid is uncertain, though a vasoconstrictor effect is thought to be most likely. Zweifelach *et al*¹⁶ have shown that the terminal vascular bed is rendered sensitive to the vasoactive drugs by steroids, suggesting that the vessels in the haemangioma may be sensitised to naturally occurring vasoactive amines by local steroid injections. This would imply that steroids are simply accelerating the natural involutional process.

Only two of the lesions in this series were examined by biopsy and it is therefore difficult to comment on the relative response of either the capillary or the cavernous portion of the haemangioma (the classification being based

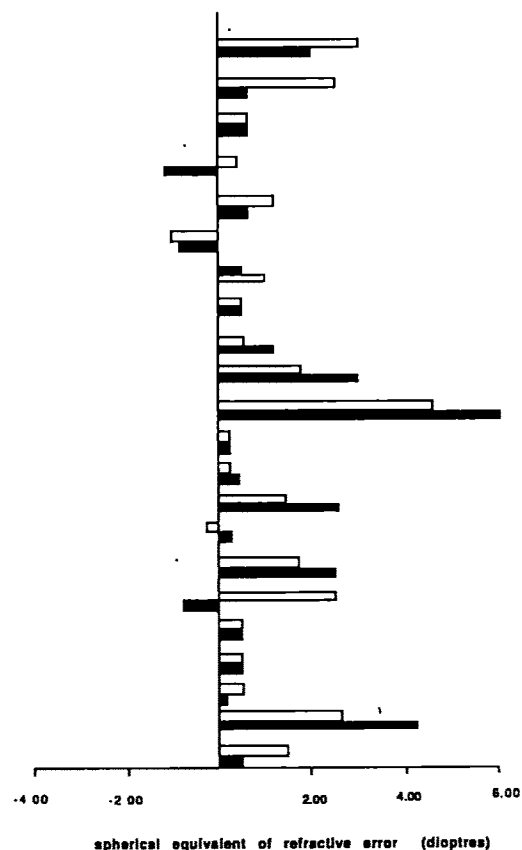


Figure 2 The spherical equivalent of refractive error in patients with an adnexal haemangioma. White bars: uninvolved eye. Black bars: eye with haemangioma.

on the calibre of the predominant vascular channels present in the haemangioma¹⁷). In previous reports only the haemangioendothelioma has been thought to be less responsive to treatment,¹¹ and this may explain why the two children in this series failed to respond.

This study lends support to the view that loss of visual function in these children is usually the result of induced refractive change, rather than obstruction of the visual axis or strabismus.

Anisometropia was present in 68% of children (15 of 22) with adnexal haemangiomas. We did not find myopia to be a common refractive error, but did note a high incidence of asymmetric astigmatic errors. Upper lid lesions carried a high risk of astigmatism, with only two out of 14 patients showing no such error. Lower lid lesions were less likely to lead to astigmatism, though this was not invariable with one haemangioma leading to 2.00 dioptres of astigmatism. In every case the axis of astigmatism (plus convention) was found to point towards the haemangioma.

Similar findings have been reported with haemangiomas by Robb⁷ and for varied adnexal masses by Bogan *et al*.¹⁸ Robb concluded on the basis of keratometry readings that the astigmatic component of the refractive error originated in the cornea. It is known that the maximum rate of change in the corneal radius of curvature following birth occurs in the first year of life.¹⁹ A difference of less than 0.1 mm between the principal radii of curvature of the cornea will cause an astigmatism of 0.50 dioptre. It would therefore seem possible that the refractive error associated with haemangiomas, which appear within the first two months of life, is induced by pressure of the lesion leading to a mechanical distortion of the cornea.

Studies of children with normal eyes by techniques of near retinoscopy,²⁰ cycloplegic retinoscopy,²¹ and photorefractometry²² have demonstrated a higher incidence of astigmatism in infants than adults. The predominant axis of the positive cylinder remains controversial,^{21,23} though there is agreement that the astigmatism decreases and has largely disappeared by school age (4 to 5½ years of age). The possibility that the astigmatic errors we have recorded reflect the normal astigmatism of infancy is small, because in each case the axis of astigmatism was related to the location of the haemangioma.

In contrast to the studies on normal infant eyes in which astigmatism was shown to decrease over the first five years of life Robb⁷ found that astigmatism associated with haemangiomas persisted despite resolution of the lesion. Only two out of 16 patients lost astigmatism during observation – one at 1 year of age and one at 8 years of age. Astigmatism persisted in 11 beyond 6 years and in six beyond 12 years. He concluded that a permanent corneal change had resulted from the presence of the haemangioma. A review of 14 children seen in this unit before the introduction of steroid injection has also shown this failure of the astigmatism to disappear spontaneously in children with haemangiomas (unpublished data).

In those of our children who had an astigmatic error and responded to treatment with local steroids, we noted a marked reduction of

astigmatism in 53.8% (seven of 13), a lesser reduction in 15.4% (two of 13), and no reduction in 30.8% (four of 13). These results may in fact simply reflect a return to the rate of spontaneous reduction in astigmatism that might be expected in unaffected children, though greatly exceeding the rate of reduction seen with untreated haemangiomas. It cannot, however, be argued that successful treatment of the haemangioma removes the risk of amblyopia and therefore regular refraction and visual assessment remain necessary.

No serious complications were seen in this study. Reported complications, however, include eyelid necrosis,²⁴ permanent subcutaneous fat atrophy,²⁵ and central retinal artery occlusion²⁶ – presumed to be due to retrograde arterial flow leading to embolism of steroid suspension in the central retinal artery. We believe these risks can be minimised by accurate injection technique at multiple sites in the lesion, taking care to avoid direct injection into the vascular channels by drawing back on the syringe before injection. In addition the potential for adrenal suppression and the risks of a general anaesthetic exist. Although the dosages used might potentially lead to transient suppression of cortisol levels,²⁷ the half life of the steroid regimen used is less than 30 hours and we observed no major systemic effects. We found only one case of subcutaneous fat atrophy which resolved over a period of six months.

Conclusion

Intralesional injection of steroids is an effective way of managing haemangiomas in children. Most respond to one or two injections within a period of two to four months and achieve a satisfactory resolution of the lesion. In view of the high incidence of visual disability associated with vascular hamartomas and the possibility that treatment may have a role in reversing the high rate of induced astigmatism found, we would suggest treatment is carried out at an early stage for any lesion thought likely to lead to anisometropia, strabismus, or lid closure. Particular attention should be paid to children with a haemangioma of the upper lid, and follow-up refraction and visual assessment are essential.

- 1 Jacobs AH, Walton RG. The incidence of birthmarks in the neonate. *Pediatrics* 1976; 58: 218–22.
- 2 Bivings L. Spontaneous regression of angiomas in children. *J Pediatr* 1954; 45: 643–7.
- 3 Bowers RE, Graham EA, Tomlinson KA. The natural history of the strawberry naevus. *Arch Dermatol* 1960; 82: 667–80.
- 4 Haik BG, Jakobiec FA, Ellsworth RM, Jones IS. Capillary hemangioma of the lids and orbit: an analysis of the clinical features and therapeutic results in 101 cases. *Ophthalmology* 1979; 86: 760–89.
- 5 Stigmar G, Crawford JS, Ward CM, Thompson HG. Ophthalmic sequelae of hemangiomas of the eyelids and orbit. *Am J Ophthalmol* 1978; 85: 806–13.
- 6 Deady JP, Willshaw HE. Vascular hamartomas in childhood. *Trans Ophthalmol Soc UK* 1986; 105: 712–6.
- 7 Robb RM. Refractive errors associated with hemangiomas of the eyelids in infancy. *Am J Ophthalmol* 1977; 83: 52–8.
- 8 Henderson JS. *Orbital tumors*. Philadelphia: Saunders, 1973: 139.
- 9 Kushner BJ. Local steroid therapy in adnexal hemangioma. *Ann Ophthalmol* 1979; 11: 1005–9.
- 10 Zak AT, Morin DJ. Early local steroid therapy of infantile eyelid hemangiomas (local steroid therapy of eyelid hemangiomas). *J Paediatr Ophthalmol Strabismus* 1981; 18: 25–7.
- 11 Kushner BJ. Intralesional corticosteroid injection of infantile adnexal hemangioma. *Am J Ophthalmol* 1982; 93: 496–506.

- 12 Willshaw HE, Deady JP. Vascular hamartomas in childhood. *J Pediatr Surg* 1987; 22: 281-3.
- 13 Kushner BJ. The treatment of periorbital infantile hemangioma with intralesional corticosteroid. *Plast Reconstr Surg* 1985; 76: 517-24.
- 14 Fielder AR, Moseley MJ. Do we need to measure the vision of children. *J R Soc Med* 1988; 81: 380-3.
- 15 Jampolsky A. In: Crawford JS, Flynn JT, Haik BG, et al, eds. *Pediatric ophthalmology and strabismus*. Trans New Orleans Acad Ophthalmol New York: Raven, 1981: 441-2.
- 16 Zweifach BW, Shore E, Black MM. The influence of the adrenal cortex on behaviour of the terminal vascular bed. *Ann NY Acad Sci* 1953; 56: 626-33.
- 17 Rooke A, Wilkinson DS, Ebling FJG. *Textbook of dermatology*. Philadelphia: Davis, 1968.
- 18 Bogan S, Simon JW, Krohel GB, Nelson LB. Astigmatism associated with adnexal masses in infancy. *Arch Ophthalmol* 1987; 105: 1368-70.
- 19 Weale RA. *A biography of the eye*. London: Lewis, 1982: 103.
- 20 Gwaizda J, Scheiman M, Mohindra I, Held R. Astigmatism in children: changes in axis and amount from birth to six years. *Invest Ophthalmol Vis Sci* 1984; 25: 88-92.
- 21 Dobson V, Fulton AB, Sebris SL. Cycloplegic refractions of infants and young children: the axis of astigmatism. *Invest Ophthalmol Vis Sci* 1984; 25: 83-7.
- 22 Howland HC, Sayles N. Photorefractive measurements of astigmatism in infants and young children. *Invest Ophthalmol Vis Sci* 1984; 25: 93-102.
- 23 Fischer FP. In: Sorsby A, ed. *Modern trends in ophthalmology*. London: Butterworth, 1984; 2: 84.
- 24 Vasquez-Botet R, Reyes BA, Vasquet-Botet M. Sclerodermiform linear atrophy after the use of intralesional steroids for periorbital hemanagiomias: a review of complications. *J Pediatr Ophthalmol Strabismus* 1989; 26: 124-7.
- 25 Droste PJ, Ellis FD, Sondhi N, Helveston EM. Linear subcutaneous fat atrophy after corticosteroid injection for capillary hemangioma. *Am J Ophthalmol* 1988; 105: 65-9.
- 26 Shorr N, Seiff SR. Central retinal artery occlusion associated with periocular injection for juvenile hemangioma. *Ophthalmic Surg* 1986; 17: 229-31.
- 27 Sutula FC, Golver AT. Eyelid necrosis following intralesional corticosteroid injection for capillary hemangioma. *Ophthalmic Surg* 1977; 18: 103-5.

Extracapsular cataract extraction with posterior chamber lens implantation in Fuchs's heterochromic cyclitis

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Abstract

Twenty-two patients with Fuchs's heterochromic cyclitis had a posterior chamber intraocular lens implanted after extracapsular cataract extraction. After a mean follow-up period of 2.5 years (range, 6 to 70 months) half the patients had a visual acuity of 1.0 or more. The results compare favourably with those in the general population.

Although Fuchs in 1906 was not the first to report patients with cataract in eyes of lighter colour than their fellows, Lawrence having preceded him in 1843, his study of 38 cases was the most extensive and established the essential features of the syndrome bearing his name: mild cyclitis, change in colour of the iris, absence of synechiae, presence of fine keratic precipitates, and the preservation of vision except for the common development of complicated cataract.

Most, if not all, patients with Fuchs's heterochromic cyclitis develop some degree of cataract.^{1,2}

It has been observed that (intracapsular) cataract extraction in these patients has a relatively good prognosis. Brückner and Meisner³ wrote in 1929 (trans): 'Operation of this form of (strictly speaking) cataracta complicata mostly has a good result. The eyes endure the operation without much reactive inflammation. . . . One must be somewhat reserved about the prognosis for vision because of the often present vitreous opacities which are not visible before the operation because of the cataract.' Their impression is supported by more recent studies,^{4,5} though less favourable results have also been published.^{6,7}

Little is known about the additional risks of intraocular lens implantation in these patients. Following the recent study of Gee and Tabbara⁸ we report here a retrospective analysis of the visual acuity results as well as the surgical and postoperative complications in 22 patients with Fuchs's heterochromic iridocyclitis who underwent an extracapsular cataract extraction with implantation of a posterior chamber intraocular lens.

Patients and methods

The population of the Uveitis Polyclinic of the Rotterdam Eye Hospital was screened for all patients who met the following criteria: (1) Fuchs's heterochromic cyclitis; (2) extracapsular cataract extraction with implantation of a posterior chamber intraocular lens; (3) no previous surgery; and (4) a minimal follow-up period of six months.

Thirty-eight patients with Fuchs's heterochromic cyclitis had to be excluded. Four underwent an intracapsular cataract extraction with or without lens implantation; seven had an extracapsular cataract extraction without lens implantation; in two the follow-up period was too short; and the remaining 25 patients were not operated on at all. We finally obtained 22 patients, and our retrospective analysis is based on them.

All patients were admitted to hospital and received indomethacin and phenylephrin eye-drops one day preoperatively. Surgery was under local anaesthesia in three patients and under general anaesthesia in the other 19 patients.

After preparation of a fornix based conjunctival flap, limbal incision, capsulotomy, nuclear expression, and manual aspiration/irrigation of the remaining cortex, a Pearce one-piece polymethylmethacrylate (PMMA) posterior chamber lens was inserted. In 14 patients sodium hyaluronate (Healonid) was used during capsulotomy and at the time of lens insertion. The incision was closed with one 10-0 nylon running suture. In some patients surgery was completed with a parabolbar injection of gentamicin 20 mg in combination with betamethasone 4 mg.

Postoperatively all patients were treated with indomethacin eyedrops and gentamicin/dexamethasone eyedrops, both three times a day. All patients were discharged on the fourth postoperative day.

Results

Twenty-two patients received a posterior chamber intraocular lens after extracapsular extraction. The group consisted of nine women and 13 men, ranging in age from 14 to 81 years, mean 42 years. Most patients had a posterior subcapsular type of cataract. Preoperative visual acuity ranged from light perception to 0.5. Fourteen patients had a visual acuity of less than 0.1. One patient used antiglaucoma eyedrops prior to operation.

Patients have been followed up for six to 70 months, mean 32 months, after operation. The preoperative follow-up ranged from three to 20 years, mean 10 years.

After extracapsular cataract extraction with posterior chamber intraocular lens implantation the visual acuity improved in all patients except one. Eleven patients (50%) obtained a visual acuity of 1.0 or more, while in three patients (14%) visual acuity was less than 0.5 at the last follow-up visit.

As regards surgical and postoperative complications (Table 1), we observed two patients with small transient anterior chamber

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Table 1 Surgical and postoperative complications (%)

Complication	A*	B	C	D
Anterior chamber haemorrhage	9	13	4	1.3
Vitreous loss/capsular rupture	5	0	0	2-4
Miosis	9	-	-	-
Posterior capsule opacification	18	-	4	15
Postoperative glaucoma	9	0	0	0.5
Posterior synechiae	14	0	19	2.0
Clinical persistent cystoid macular oedema	0	0	22	0.6
Retinal detachment	0	0	0	1-1.5
Endophthalmitis	0	0	0	0.2
Postoperative VA less than 0.5	5	0	15	5-10
Postoperative VA 1.0 or more	50	27	26	65
Fibrinous reaction	5	0	-	0.6

*A: Eye Hospital 1990, n=22. B: Gee and Tabbara,⁹ n=15: Fuchs's heterochromic cyclitis. C: Foster *et al.*,¹⁰ n=27: other types of uveitis. D: Fagadau *et al.*,¹¹ Guzek *et al.*,¹² Stark *et al.*,¹³ Smith *et al.*,¹⁴ Ohloff *et al.*,¹⁵ O'Donnell and Santos:¹⁶ general population.

haemorrhages during surgery. In two patients there was a positive vitreous pressure, and in one patient a capsular rupture with vitreous loss. In two patients it was necessary to make an iridotomy, because it was impossible to widen the pupil sufficiently owing to previous antiglaucoma medication with miotics.

In two patients we observed a secondary glaucoma which was not present preoperatively. The pressures were well controlled by topical medication. Ten patients developed some degree of posterior capsule opacification. In four of them this was successfully treated with Nd-YAG laser capsulotomy. In four patients there was impairment of visual acuity (to the level of 0.4 to 0.5) due to vitreous opacities. One patient had a postoperative visual acuity of 0.1 because of visual field loss due to glaucoma.

We did not encounter any case of retinal detachment, endophthalmitis, or persistent clinical cystoid macular oedema.

Discussion

Cataract is one of the most prominent signs of Fuchs's heterochromic cyclitis. So much so that Fuchs in his textbook discussed it in a chapter about diseases of the lens and called it: 'Cataracta in oculo coeruleo oder heterochromiekatarakt'.

In an attempt to answer the question: Is extracapsular cataract extraction with implantation of a posterior chamber intraocular lens a justifiable procedure in patients with Fuchs's heterochromic cyclitis? we compared our results with the results of extracapsular cataract extraction with posterior chamber lens implantation in other series of patients.

We selected three kinds of studies: patients with Fuchs's heterochromic cyclitis,⁹ patients with other types of uveitis,¹⁰ and patients from the general population.¹¹⁻¹⁶ A comparison with intracapsular operated patients was not done.

The final visual acuity in our patients is comparable with that of the general population. Half our patients achieved a visual acuity of 1.0 or more versus 65% of the general population. But in Fuchs's heterochromic cyclitis there is an increased risk of anterior chamber haemorrhage, postoperative glaucoma, posterior synechiae, and a postoperative fibrinous reaction. The

anterior chamber haemorrhage (Amsler's sign) was in both cases small and transient. It never interfered with the operation. In two patients who needed an iridotomy, miosis was due to previous antiglaucoma medication. The high incidence of postoperative glaucoma is in our opinion not related to surgery, since in the natural course of Fuchs's heterochromic cyclitis 15-18% patients develop glaucoma.¹² We cannot explain the occurrence of posterior synechiae after surgery.

Our group of patients is probably too small to detect any increased risk for persistent cystoid macular oedema, retinal detachment, or endophthalmitis as compared with the incidence in the general population.

It is difficult to compare our results with those in patients with other types of uveitis. Foster *et al.*¹⁰ did an extracapsular cataract extraction with intraocular lens implantation in 27 patients with uveitis, including one patient with Fuchs's heterochromic cyclitis. The postoperative visual acuity was 1.0 or more in only 26% of the patients. There was also a relatively high incidence of persistent clinical cystoid macular oedema. So the visual prognosis after cataract surgery seems to be better in patients with Fuchs's heterochromic cyclitis than in patients with other types of uveitis. One has to take into account, however, that all the patients reported on by Foster *et al.*¹⁰ had a visual acuity of 0.1 or less preoperatively.

When we compare our results with those of Gee and Tabbara,⁹ the most striking difference is the better visual outcome. There are at least two possible explanations for this. First, all our patients had an intraocular lens implanted, while a third of their patients did not; and, secondly, there was a difference in preoperative visual acuity. 68% of our patients had a preoperative visual acuity of 0.1 or less versus 93% of their patients.

CONCLUSION

Implantation of a posterior chamber intraocular lens is a justified procedure after extracapsular cataract extraction in patients with Fuchs's heterochromic cyclitis. It does not constitute an additional risk. Or in the words of Fuchs himself (trans)¹⁷: 'These cases are generally not complicated by underlying disease and can be operated upon with good results'.

- 1 Dernouchamps JP. Fuchs' heterochromic cyclitis: an IUSG study about 550 cases. In: Saari KM, ed. *Uveitis update*. Amsterdam: Excerpta Medica, 1984: 129-35.
- 2 Loewenfeld IE, Thompson HS. Fuchs' heterochromic cyclitis: a critical review of the literature. I. Clinical characteristics of the syndrome. *Surv Ophthalmol* 1973; 17: 394-457.
- 3 Brückner A, Meisner W. *Grundriss der Augenheilkunde*. 2nd ed. Leipzig: Thieme, 1929.
- 4 Smith R, O'Connor R. Cataract extraction in Fuchs syndrome. *Arch Ophthalmol* 1974; 91: 39-42.
- 5 Mills KB, Rosen ES. Intraocular lens implantation following cataract extraction in Fuchs' heterochromic uveitis. *Ophthalmic Surg* 1982; 13: 467-9.
- 6 Liesegang TJ. Clinical features and prognosis in Fuchs' uveitis syndrome. *Arch Ophthalmol* 1982; 100: 1622-6.
- 7 Ward DM, Hart CT. Complicated cataract extraction in Fuchs' heterochromic uveitis. *Br J Ophthalmol* 1967; 51: 530-8.
- 8 Norn MS. Cataract extraction in Fuchs' heterochromia. *Acta Ophthalmol (Kbh)* 1968; 46: 685-99.
- 9 Gee SS, Tabbara KH. Extracapsular cataract extraction in Fuchs' heterochromic iridocyclitis. *Am J Ophthalmol* 1989; 108: 310-4.

- 10 Foster CS, Fong LP, Singh G. Cataract surgery and intraocular lens implantation in patients with uveitis. *Ophthalmology* 1989; 96: 281-8.
- 11 Fagadau WR, Maumenee AE, Stark WJ, Dattiles M. Posterior chamber intraocular lenses at the Wilmer Institute: a comparative analysis of complications and visual results. *Br J Ophthalmol* 1984; 68: 13-8.
- 12 Guzek JP, Holm M, Cotter JB, et al. Risk factors for intraoperative complications in 1000 extracapsular cataract cases. *Ophthalmology* 1987; 94: 461-6.
- 13 Stark WJ, Maumenee AE, Fagadau W, et al. Cystoid macular edema in pseudophakia. *Surv Ophthalmol* 1984; 28 (suppl): 442-51.
- 14 Smith PW, Stark WJ, Maumenee AE, et al. Retinal detachment after extracapsular cataract extraction with posterior chamber intraocular lens. *Ophthalmology* 1987; 94: 495-504.
- 15 Ohrlöf C, Dardenne MU, Konen C, Sherif A. Erfahrungen mit den ersten 1400 Hinterkammerlinsenimplantationen nach Phacoemulsifikation. *Klin Monatsbl Augenheilkd* 1982; 181: 253-6.
- 16 O'Donnell FE, Santos B. Posterior capsular-zonular disruption in planned extracapsular surgery. *Arch Ophthalmol* 1985; 103: 652-3.
- 17 Fuchs E. *Lehrbuch der Augenheilkunde*. 16th ed. Vienna: Deuticke, 1939.

FIFTY YEARS AGO

A case of blue sclerotics

This case of blue sclerotics may be of interest to your readers. The association of deafness and liability to fracture of bones is well known, but there is some doubt as to whether the sclera is thin and so the choroid shows through, or is of normal thickness but transparent.

There was a history of deafness of the left ear of long standing, and of recent fractures of the femur on stepping off an omnibus. As far as she knows, none of her relatives is deaf, has blue sclerotics, or has sustained fractures. The patient was brought to me by her doctor, as she had almost lost the vision of her left eye. On examination the blue sclerotics in both eyes were very noticeable, the vision of the right eye was 6/6, and of the left perception of light only. The tension of the right eye was normal, but

that of the left was raised considerably. The field of vision of the right eye was normal. The patient is aged 46 years.

As the tension did not lessen with the use of miotics, I decided to trephine the left eye. Though I expected the sclera might be thin, I was surprised to find how very thin it proved to be. One complete turn of the Elliot's trephine was sufficient to cut through.

My object in reporting this case is not to discuss the treatment of the glaucoma, but to draw attention to the thinness of the sclera, and to the absence of stretching of the sclera with such an increased tension in an eye with so thin an outer coat. — Spencer Walker JP.

Br J Ophthalmol 1941; 25: 383.

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MINI REVIEW

Adhesives in retinal detachment surgery

Methods of break sealing have not changed significantly since Gonin devised the operation of ignipuncture using scleral cautery, as all current techniques rely on the production of a thermally induced inflammatory lesion which heals to form a chorioretinal scar. The treated break has to be closed against the retinal pigment epithelium while healing is taking place, which in simple detachments is usually achieved by scleral indentation. In complicated cases where vitrectomy has been performed and in selected simple detachments an internal tamponading agent is required to close the retinal break while the chorioretinal scar develops. Internal tamponade with gas and air can be complicated by cataract formation, raised intraocular pressure, or secondary glaucoma. Silicone oil causes cataract, glaucoma, and keratopathy in a considerable proportion of cases, and most develop refractive errors and emulsification. Early removal of silicone oil helps to reduce the incidence of some of these complications and makes them easier to manage, but retinal redetachment occurs in 12-30% of eyes. In addition, cryotherapy has been implicated in the pathogenesis of proliferative vitreoretinopathy, as it induces breakdown of the blood-retinal barrier, causes a localised inflammatory response, and disperses viable retinal pigment epithelial cells into the vitreous cavity.

Several adhesives have been tried as a novel, non-inflammatory means of creating chorioretinal adhesion for selected complicated detachments. Their main advantage is that break sealing would occur immediately, making internal tamponade largely unnecessary. The adhesives that have been evaluated include cyanoacrylates, fibrin, mussell glue, and other synthetic and biological compounds. Some of these adhesives have already found a place in the management of certain anterior segment conditions.

The cyanoacrylates are a group of adhesives formed by the condensation of cyanoacetates and formaldehyde, which rapidly polymerise on contact with anions. During polymerisation heat is produced, and during hydrolytic degradation formaldehyde is released. Brooks McCuen is currently championing the use of cyanoacrylates in retinopexy, and he uses N-butylcyanoacrylate (Histoacryl), which has been shown to be less toxic than methylcyanoacrylate. Minute drops of the adhesive are applied to the edge of flattened retinal breaks after vitrectomy, fluid/air exchange, and drying of the retinal surface. The adhesive is mixed with iophendylate, which slows polymerisation, and is delivered with a specially designed applicator which prevents the adhesive from polymerising within the delivery system. In preliminary animal work Histoacryl produced strong, immediate, and permanent adhesion between the retina and retinal pigment epithelium,¹ but localised retinal necrosis developed round the drop of adhesive. Affected retina either developed full thickness retinal holes or became atrophic.² These findings were more pronounced in silicone oil filled eyes,³ which could be due either to an insulating effect or to localisation of toxic products.

So far 34 patients have been treated with Histoacryl, with good surgical results.^{4,5} It appears that the human retina is less susceptible to cyanoacrylate toxicity than the rabbit retina, though two eyes developed periadhesive retinal holes. McCuen currently advocates the use of cyanoacrylate retinopexy for the management of complicated retinal detachments

that have been refractory to other forms of treatment and to avoid the complications of internal tamponade with silicone oil.

Fibrin, made from either autologous plasma, human or autologous fibrinogen, and bovine thrombin, has also been used experimentally and clinically. In experimental animal models fibrin has been shown to be non-toxic, but it produces only temporary adhesion because the fibrin clot readily lyses despite the addition of aprotinin, a proteolytic enzyme that delays fibrinolysis. Fibrin retinopexy has also been associated with the formation of epiretinal membranes when used in the rabbit. Coleman has treated seven patients with macular holes and giant retinal tears, and he applied the adhesive to the edge of the break after vitrectomy with peroperative retinal flattening and fluid-air exchange. The retina became reattached in three of the four eyes with macular holes, but none of the giant retinal tears remained flat postoperatively. No complications that could be attributable to the fibrin were noted after surgery.⁶

Other adhesives that have been evaluated for retinopexy in an experimental setting are mussell protein, transforming growth factor beta (TGF- β), acetate polymers, and polysiloxanes. The latter are adhesives used in dentistry. The acetate polymer looks promising, as it gives good adhesion between the retinal pigment epithelium and retina and is not toxic.⁷ The polysiloxane adhesive has the advantage that it can be delivered in an aqueous environment, but it causes a localised granulomatous tissue reaction.⁸ Mussell glue has also undergone preliminary evaluation in an animal model. The foot of the mussell bivalve attaches itself to underlying substrates via a bysuss thread, using a powerful two-component proteinaceous adhesion. Natural, extracted adhesive and protein manufactured by bioengineering techniques are both available, though they have not yet passed FDA regulations. Preliminary studies show that this adhesive may prove of value in retinopathy, as it is not toxic nor does it stimulate an inflammatory reaction when injected into the vitreous cavity.⁹ TGF- β has been delivered to retinal breaks in a hyaluronic acid vehicle, where it stimulated a localised wound healing response with sealing of retinal breaks.¹⁰ Although breaks were sealed with TGF- β , as with cryotherapy, a time factor is involved, and internal tamponade would still be necessary.

Despite considerable research the ideal adhesive remains elusive as those evaluated to date are either toxic, difficult to deliver, provide only transient adhesion, depend on a cellular wound healing response, or stimulate an inflammatory reaction with epiretinal membrane formation. The ideal adhesive would be readily available, easy to prepare, store, and sterilise and also be easy to apply to the retinal-RPE surface. Some of the problems of delivery would be avoided if a one-component adhesive were available that had a polymerisation time that could be manipulated. The adhesive would have to provide permanent adhesion or stimulate a purely localised wound healing response, be non-toxic and non-inflammatory. If a suitable adhesive could be found, the management of selected complicated detachments would be simplified and the complications related to cryotherapy and internal tamponade avoided.

CLARE E GILBERT

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- 1 McCuen BW, Hida T, Sheta SM, Isbey EK, Hahn DK, Hickingbotham D. Experimental transvitreal cyanoacrylate retinopathy. *Am J Ophthalmol* 1986; 102: 199-207.
- 2 Hida T, Sheta SM, Proia AD, McCuen BW. Retinal toxicity of cyanoacrylate tissue adhesive in the rabbit. *Retina* 1988; 8: 148-53.
- 3 Sheta SM, Hida T, McCuen BW. Experimental transvitreal cyanoacrylate retinopathy through silicone oil. *Am J Ophthalmol* 1986; 102: 717-22.
- 4 McCuen BW, Hida T, Sheta SM. Transvitreal cyanoacrylate retinopathy in the management of complicated retinal detachments. *Am J Ophthalmol* 1987; 104: 127-32.
- 5 Sheta SM, Hida T, McCuen BW. Cyanoacrylate tissue adhesive in the management of recurrent detachment caused by macula hole. *Am J Ophthalmol* 1990; 109: 28-32.
- 6 Coleman DJ, Lucas BC, Fleischmann JA, Dennis PH, Chang S, Iwamoto T, Nalbandian RM. A biologic tissue adhesive for vitreoretinal surgery. *Retina* 1988; 8: 250-6.
- 7 Sobol WM, Campbell JV, Koutz C, Holz E, Parke DW. Transvitreal retinopathy using acetate polymers. *Invest Ophthalmol Vis Sci* 1989; 30 (suppl) 12.
- 8 Prince KJ, Nielson S, Abren RB, Liggett PE. Preliminary evaluation of polysiloxanes for experimental retinopathy. *Invest Ophthalmol Vis Sci* 1989; 30 (suppl) 12.
- 9 Liggett PE, Cano M, Green RL, Lean JS, Rao NA. Intraocular inflammatory and toxic effects of a new tissue adhesive for retinopathy: mussell adhesive protein. *Invest Ophthalmol Vis Sci* 1987; 28 (suppl) 206.
- 10 Smiddy WE, Glaser BM, Green WR, Connor TB, Roberts AB, Lucas R, Sporn MB. Transforming growth factor beta. A biologic chorioretinal glue. *Arch Ophthalmol* 1989; 107: 577-80.

CASE REPORTS

Clearance of corneal crystals in nephropathic cystinosis by topical cysteamine 0.5%

Nicholas P Jones, Robert J Postlethwaite, Joan L Noble

Abstract

A 2-year-old girl with nephropathic cystinosis was successfully treated with topical cysteamine 0.5% to one eye. Clearance of crystals from the treated cornea was virtually complete after three months. The possibilities and limitations of this form of treatment are discussed.

Infantile nephropathic cystinosis is an autosomal recessive condition leading to the progressive accumulation of cystine in tissues including the eye.¹ Characteristic crystal deposition within the cornea and conjunctiva leads to intense photophobia and visual disability.² Later, crystal deposition in the iris, on the lens capsule, and within the retina³ further affects vision. The use of oral cysteamine has been shown to reduce cystine deposition systemically and to improve renal function⁴ but an effect on the cornea has not been demonstrated. Trials of topical cysteamine have shown variable response to treatment,^{5,6} with a minority of patients showing substantial clearance of crystals over treatment periods ranging from four to 37 months. We report on a child with nephropathic cystinosis who, with good compliance to intensive treatment, obtained

excellent corneal clearance of crystals within three months from an initial, severely affected state.

Case report

The patient, a 2-year-old girl, had typical ocular signs of nephropathic cystinosis, with severe crystal deposition within the cornea and conjunctiva. The corneal stroma was more deeply involved at the periphery but involved at least the anterior half at the visual axis (Fig 1). There was intense photophobia. The signs were symmetrical.

Topical 0.5% cysteamine drops were instilled into the right eye only, hourly during waking hours. Treatment was performed by the patient's mother, who was highly motivated, and compliance was considered to be excellent. After three months the eyes were re-examined by the same observer (NPJ). The crystals were completely cleared from the axis of the right cornea. Clearance was substantial, but not complete, from the peripheral cornea (Fig 2). The diminution in photophobia during anterior segment photography was obvious. The left cornea was unchanged from its appearance three months previously. Treatment to the left eye has now



Figure 1 Right cornea before treatment, showing typical severe crystal deposition.



Figure 2 Right cornea after treatment for three months, showing virtually complete clearance of crystals except in the extreme periphery.

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given a similar result, and we aim to find a maintenance dose which is both effective and acceptable to the patient.

Discussion

The symptoms of photophobia and glare disability in nephropathic cystinosis can be disabling.^{2,3,6} Increased survival time following the use of systemic cysteamine, or after renal transplantation, makes the long-term ocular effects of great significance.³ Corneal transplantation has been used for intractable symptoms,⁷ yet crystals may quickly accumulate again after such intervention.⁴ An effective long-term topical therapy is clearly desirable.

The results of topical cysteamine therapy have been generally disappointing.^{5,6} Most patients studied by Kaiser-Kupfer *et al* did not show any discernible effect of treatment, but cysteamine 0.5% appeared more effective than 0.1%.⁶ Compliance is clearly a problem with hourly administration of drops, but it is likely that such frequency will not be required for maintenance treatment once the cornea has been cleared. The time taken to clear the cornea is probably related to the initial severity of crystal deposition. Our patient demonstrates that with good compliance with hourly drops of 0.5% cysteamine an excellent result can be obtained. If problems with compliance in long-term therapy are

encountered, it may be that a sustained-release fornix-held preparation would prove useful.

No problems with ocular toxicity have been noted with 0.5% cysteamine,⁹ yet large-dose systemic administration has been shown to be cataractogenic.¹⁰ Since, to be effective, topical cysteamine therapy would be required for life in patients with cystinosis, the long-term effects of such treatment require further evaluation.

We are grateful to Mr A Prest for the production of the illustrations.

- 1 Melles RB, Schneider JA, Rao NA, Katz B. Spatial and temporal sequence of corneal crystal deposition in nephropathic cystinosis. *Am J Ophthalmol* 1987; 104: 598-604.
- 2 Katz B, Melles RB, Schneider JA. Glare disability in nephropathic cystinosis. *Arch Ophthalmol* 1987; 105: 1670-1.
- 3 Kaiser-Kupfer MI, Caruso RC, Minkler DS, Gahl WA. Long-term manifestations in nephropathic cystinosis. *Arch Ophthalmol* 1986; 104: 706-11.
- 4 Gahl WA, Reed GF, Thoene JG, *et al*. Cysteamine therapy for children with nephropathic cystinosis. *N Engl J Med* 1987; 316: 971-7.
- 5 Kaiser-Kupfer MI, Fujikawa L, Kuwabara T, Jain S, Gahl WA. Removal of corneal crystals by topical cysteamine in nephropathic cystinosis. *N Engl J Med* 1987; 316: 775-9.
- 6 Kaiser-Kupfer MI, Gazzo MA, Datiles MB, Caruso RC, Kuehl EM, Gahl WA. A randomised placebo-controlled trial of cysteamine eye drops in nephropathic cystinosis. *Arch Ophthalmol* 1990; 108: 689-93.
- 7 Kaiser-Kupfer MI, Datiles MB, Gahl WA. Corneal transplant in a twelve-year-old boy with nephropathic cystinosis. *Lancet* 1987; i: 331.
- 8 Katz B, Melles RB, Schneider JA. Recurrent crystal deposition after keratoplasty in nephropathic cystinosis. *Am J Ophthalmol* 1987; 104: 190-1.
- 9 Jain S, Kuwabara T, Gahl WA. Range of toxicity of topical cysteamine in rabbit eyes. *J Ocul Pharmacol* 1988; 4: 127-31.
- 10 Truong T, Sagar SM, Millard WJ, Shaw JL. Cysteamine induces cataracts in newborn rats. *Invest Ophthalmol Vis Sci* 1987; 28: 1710-3.

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Juvenile fibromatosis of the orbit: a case report with review of the literature

R Jean Campbell, James A Garrity

Abstract

Proliferation of fibrous tissues to form a localised mass with infiltrating margins may occur anywhere in the body; involvement of the orbit is rare. Children and young adults are most commonly affected. The term 'juvenile fibromatosis' is one of several synonyms. Of the two main forms of this entity, the solitary form is the more common and the prognosis is good. The multicentric form has a poor prognosis. The patient described, a 2½-year-old boy, had a solitary nodule of juvenile fibromatosis removed from the right orbit and was asymptomatic 2¾ years postoperatively.

Fibroblastic proliferations of the orbit are rare. Fibromatosis is more common in children and must be distinguished from a true malignant neoplasm. The patient described had a slowly progressive superior orbital mass shown by histology and electron microscopy to be juvenile fibromatosis. This entity is locally aggressive but does not metastasise.

Case report

CLINICAL HISTORY

A 2½-year-old boy sustained a right 'black eye' as a result of a fall. Over a six-month period right ptosis with inferior displacement of the eye occurred, and a soft mass was palpated in the superior orbit. A soft discoid mass (6×2×1 mm) was removed by incisional biopsy. The diagnosis was benign haemangioendothelioma.

Six months postoperatively, because of apparent clinical progression, the lesion was injected with 1.0 ml of 50% dexamethasone/50% betamethasone. Nine months postoperatively the patient was seen at the Mayo Clinic. On examination his visual acuity was 20/80 right eye and 20/30 left eye. The right globe was proptosed and downwardly displaced (Figs 1 and 2).

At lateral orbitotomy a firm, greyish white mass (3×2.5×1.5 cm) was removed (Fig 3).

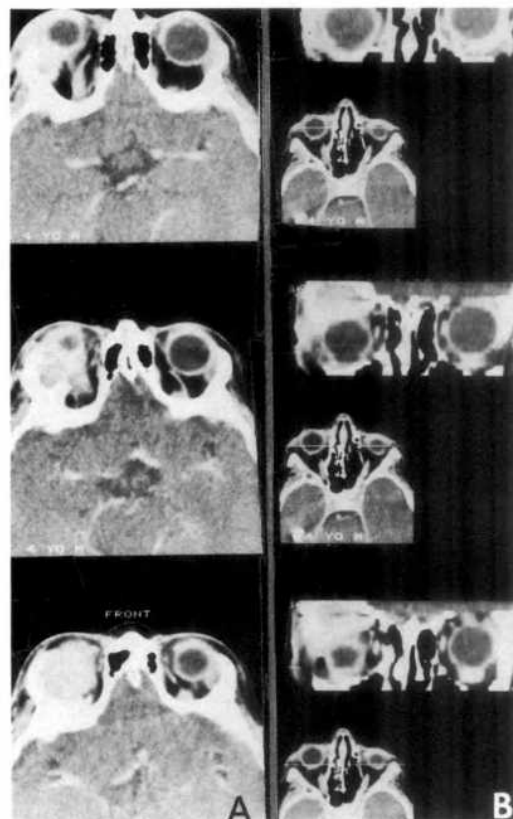


Figure 2 Axial (A) and reformatted coronal (B) computed tomography scans of orbit demonstrate a lobulated, well demarcated, enhancing, soft tissue mass within superior lateral quadrant of right orbit. There is slight retrobulbar extension and downward displacement of globe. Sclerosis and remodelling of orbital roof are noted. (B: Courtesy of the University of Minnesota, Minneapolis, Minnesota.)

PATHOLOGY

The margins were free of tumour. Tissue was fixed in 2% glutaraldehyde and 10% neutral buffered formalin. Staining techniques included haematoxylin-eosin, periodic acid Schiff with



Figure 1 The right globe has 6 mm of proptosis and is downwardly displaced 5 mm. A firm, non-tender, palpable mass was present beneath supraorbital rim. Supraduction in the right eye was severely limited.



Figure 3 Firm, greyish white mass (3×2.5×1.5 cm) removed from right orbit.

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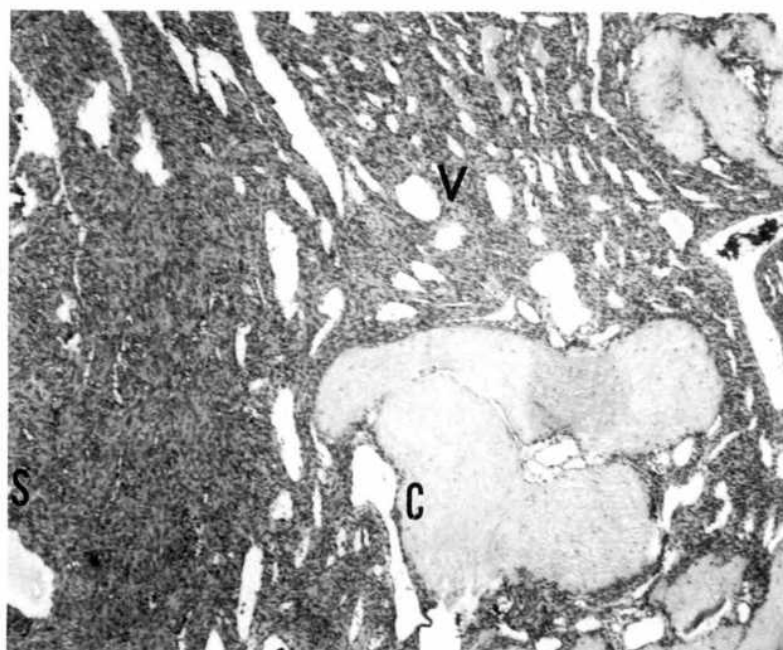


Figure 4 Cellularity varies from area to area. Solid spindle cells (S), vascular component (V), and dense collagen (C). (Haematoxylin-eosin, $\times 160$.)

and without diastase digestion, Masson trichrome, Movat pentachrome, Wilder reticulin, Mallory's phosphotungstic acid-haematoxylin, Bodian, and alcian blue.

Sections from different parts of the tumour showed variation of cellularity from area to area (Fig 4). Dense collagenous strands were present in one area; in others an admixture of spindle cells and plump fusiform cells arranged in ribbons, fascicles, and bundles was present (Fig 5). Mitotic figures were rare. Small numbers of mononuclear cells were dispersed throughout, and giant cells were randomly scattered within some of the densely cellular areas. These cells were thought to eventuate from the previous operation. Vessels were most abundant in the

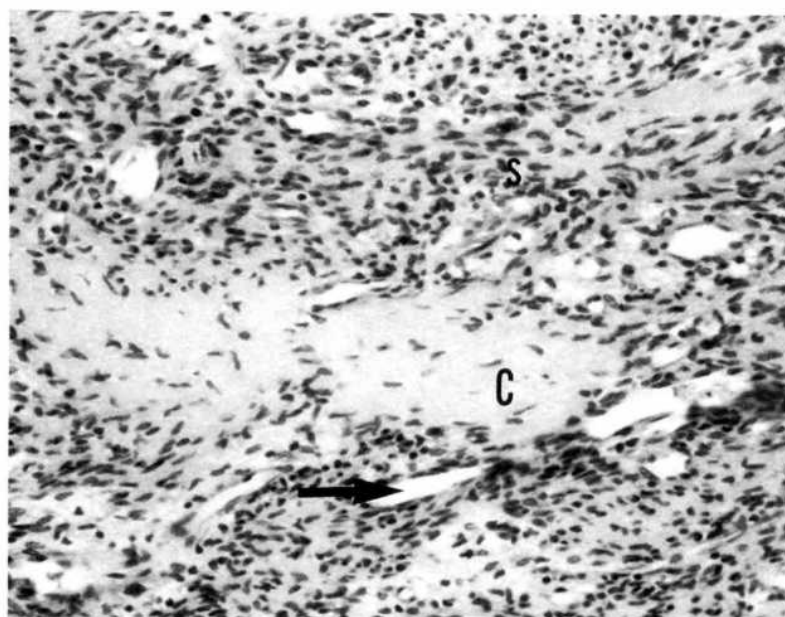


Figure 5 Spindle cells (S) intertwine. Collagen (C) is surrounded by slit-like vascular channels (arrow). (Haematoxylin-eosin, $\times 400$.)

central portion of the tumour and varied from slit-like cavities (Fig 6) and capillary channels to cavernous spaces.

The special stains confirmed that the spindle cells were fibroblasts.

Electron microscopy showed great variability of the cells from one area to another, but the fibroblast, in various degrees of differentiation, predominated (Fig 7). Many fibroblasts showed irregular dilatation of the rough-surfaced endoplasmic reticulum and fine microfilaments (Fig 8). Macrophages with membrane-bound lysosomal structures within the cytoplasm were present.

Discussion

The group of fibromatoses has been defined as consisting of non-metastasising fibrous tumours that invade locally and recur after surgical excision.^{1,2} On occasion they may regress spontaneously.³⁻⁷ Most commonly they present in early childhood and young adulthood. The histological features of those that occur in children often differ markedly from those in adults⁸ and do not always correspond with the clinical behaviour.^{3,8,9}

Stout² used the term 'juvenile fibromatosis' to include a number of entities. One of these, congenital generalised fibromatosis, has been described under various names, including diffuse congenital fibromatosis.¹⁰ The many names used reflect the histogenic hypotheses in addition to the histological picture. The term 'fibromatosis' without qualification has been used for fibrous growths that could not be included in these categories.¹¹

The subgroup of juvenile fibromatoses, namely 'congenital generalised fibromatosis,' is further subdivided^{3,12,13} into (1) a solitary form; (2) a multicentric form in which the fibrous proliferation is restricted to subcutaneous tissues, skeletal muscle, and the ends of long bones; and (3) a generalised form with visceral involvement in addition to the features of the multicentric form.³ The solitary form is the more common.^{6,10,14-16} In one study,¹⁰ 73.8% of tumours were solitary, and the term 'myofibromatosis' was used because of the histological resemblance to smooth muscle tissue. The tumour showed a preference for the head and upper part of the body, including the arm.^{6,10,11} However, only a few patients with ocular adnexal involvement have been described.^{13,17-21}

A female infant with congenital generalised fibromatosis and a large right infiltrating orbital tumour has been described.²¹ This mass also showed variation in cellular density, with marked vascularity in the peripheral areas. In a study of six children¹ five had involvement of the inferior orbital rim, with tumour extension into the lower lid in one patient. A solitary tumour localised to the zygomatic bone has been reported in a 3-month-old infant.²⁰ All these solitary lesions^{10,20} were managed by local excision.

Bilateral orbital involvement has been described in a 5-month-old boy with the congenital multicentric form of the disease.¹⁸ Fibromatosis of the cornea and limbus in association with

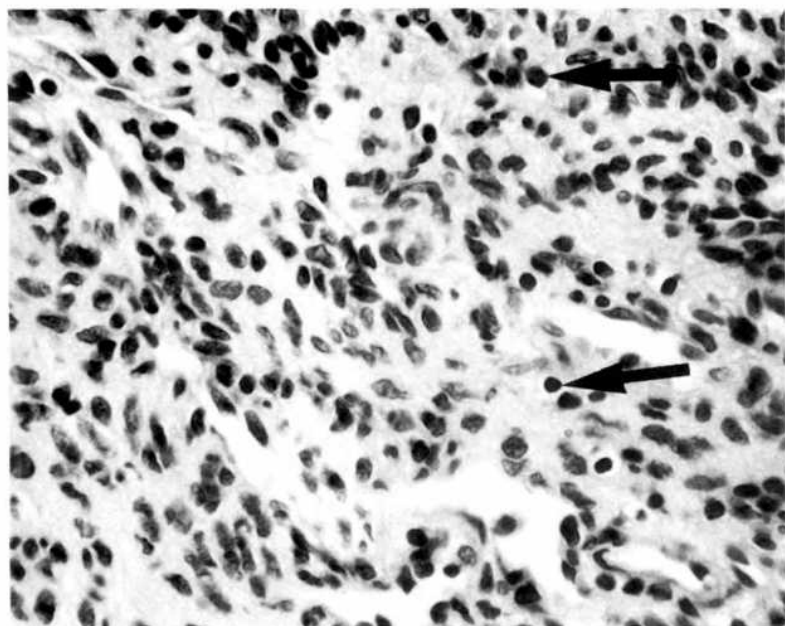


Figure 6 Central portion of tumour with spindle cells, sparse mononuclear cells (arrows), and slit-like vessels. (Haematoxylin-eosin, $\times 630$.)

congenital generalised fibromatosis has also been reported.^{17,19}

The solitary lesion averages 3 cm in diameter, is of slow growth, and has circumscribed or infiltrating edges.^{1,3,6,10,22} The histological features of the solitary and generalised forms are similar.^{6,16} Within an individual tumour the histological picture may vary from one field to another.^{1-3,6,10} For this reason needle biopsy, frozen section,^{1,23} or even incisional biopsy are inadequate and may even be misleading (Fig 4).

This variation in pattern is a characteristic. Areas composed of densely cellular spindle-shaped cells coexist with areas that are heavily vascularised, and necrotic foci may be present.¹⁰ The microscopic picture may be confused with that of other mesenchymal neoplasms.

Electron microscopic studies of solitary tumours of orbital tissue¹² and bone¹⁵ have shown that the basic tumour cell is the fibroblast in various stages of differentiation. Our studies support this finding and emphasise the wide variability from one portion of the tumour to another. Several authors have described smooth-muscle-like filaments.^{5,10}

The pathogenesis of the tumour remains unclear. Trauma is considered to be coincidental. Although familial cases have been reported in congenital generalised fibromatosis,^{4,10,24,25} none have been reported thus far in patients with ocular adnexal tumours.

In conclusion, solitary form of fibromatosis, though benign, may recur; local excision with clear margins is recommended. The diagnosis may be made by examination of several sections from different parts of the tumour. Indeed, incisional biopsy may be misleading. The combination of features suggestive of haemangiopericytoma, leiomyoma, and neurofibroma aids in the diagnosis. The variability of the cellular component as seen by light and electron microscopy emphasises the wide range of differentiation of the fibroblast. Fibromatosis may be regarded as a disease process of wide spectrum. The prognosis for the solitary form is good.

This paper was presented at the Verhoeff Society, Boston, on 13-15 April 1989.

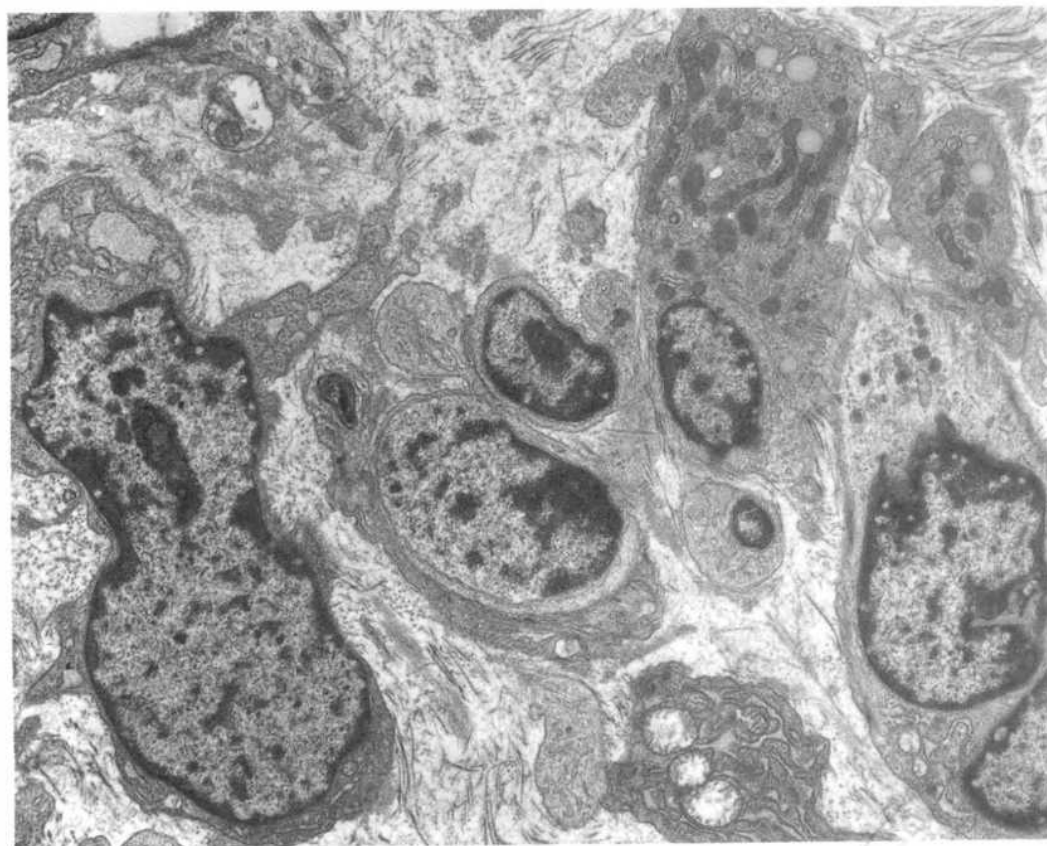


Figure 7 Electron micrograph showing fibroblasts in various degrees of differentiation. ($\times 17\,500$.)

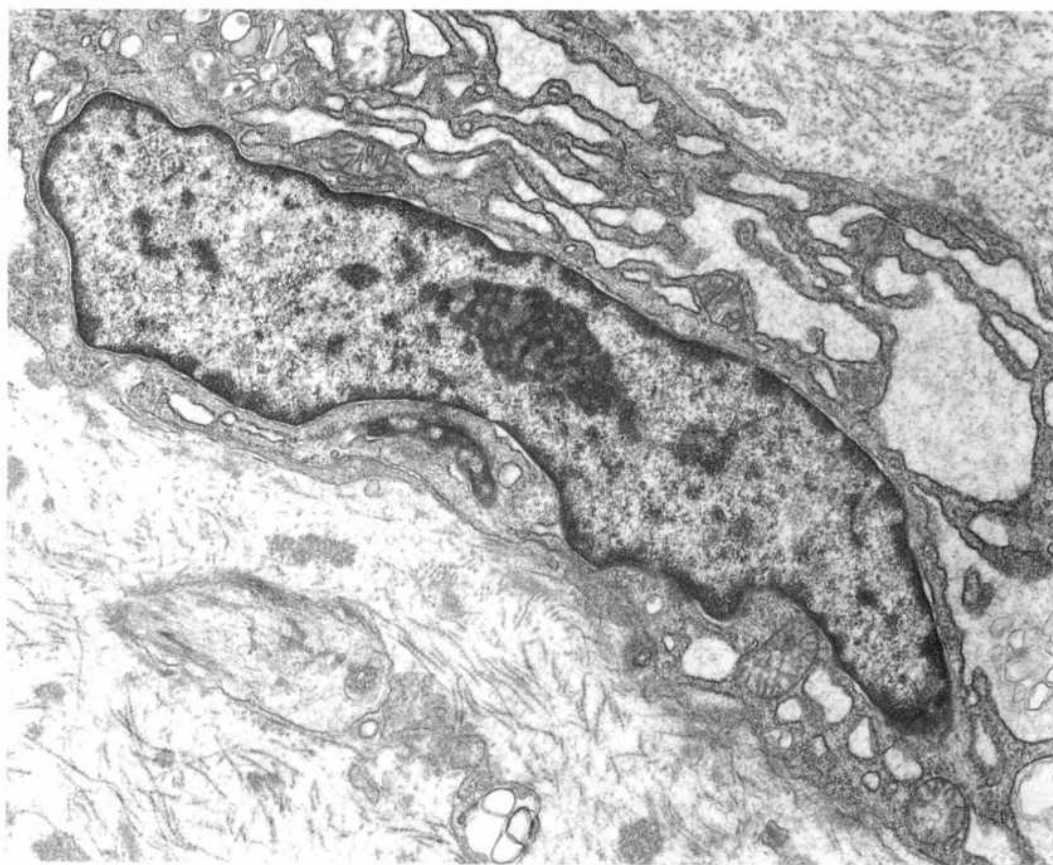


Figure 8 Electron micrograph showing fibroblast with distended, rough-surfaced endoplasmic reticulum. ($\times 37\,500$.)

- 1 Hidayat AA, Font RL. Juvenile fibromatosis of the periorbital region and eyelid: a clinicopathologic study of six cases. *Arch Ophthalmol* 1980; **98**: 280–5.
- 2 Stout AP. Juvenile fibromatoses. *Cancer* 1954; **7**: 953–78.
- 3 Baer JW, Radkowski MA. Congenital multiple fibromatosis: a case report with review of the world literature. *AJR* 1973; **118**: 200–5.
- 4 Baird PA, Worth AJ. Congenital generalized fibromatosis: an autosomal recessive condition? *Clin Genet* 1976; **9**: 488–94.
- 5 Benjamin SP, Mercer RD, Hawk WA. Myofibroblastic contraction in spontaneous regression of multiple congenital mesenchymal hamartomas. *Cancer* 1977; **40**: 2343–52.
- 6 Briselli MF, Soule EH, Gilchrist GS. Congenital fibromatosis: report of 18 cases of solitary and 4 cases of multiple tumors. *Mayo Clin Proc* 1980; **55**: 554–62.
- 7 Schaffzin EA, Chung SMK, Kaye R. Congenital generalized fibromatosis with complete spontaneous regression: a case report. *J Bone Joint Surg (A)* 1972; **54**: 657–62.
- 8 Stout AP. Fibrosarcoma in infants and children. *Cancer* 1962; **15**: 1028–40.
- 9 Chung EB, Enzinger FM. Infantile fibrosarcoma. *Cancer* 1976; **38**: 729–39.
- 10 Chung EB, Enzinger FM. Infantile myofibromatosis. *Cancer* 1981; **48**: 1807–18.
- 11 Conley J, Stout AP, Healey WV. Clinicopathologic analysis of eighty-four patients with an original diagnosis of fibrosarcoma of the head and neck. *Am J Surg* 1967; **114**: 564–9.
- 12 Kauffman SL, Stout AP. Congenital mesenchymal tumors. *Cancer* 1965; **18**: 460–76.
- 13 Moretton LB, Mueller E, Schreiber M. Generalized hamartomatosis (congenital generalized fibromatosis). *AJR* 1972; **114**: 722–34.
- 14 Chung EB. Pitfalls in diagnosing benign soft tissue tumors in infancy and childhood. *Pathol Annu* 1985; **20**: 324–5.
- 15 Kindblom L-G, Angervall L. Congenital solitary fibromatosis of the skeleton: case report of a variant of congenital generalized fibromatosis. *Cancer* 1978; **41**: 636–40.
- 16 Kindblom L-G, Termén G, Sävje-Söderbergh J, Angervall L. Congenital solitary fibromatosis of soft tissues, a variant of congenital generalized fibromatosis: two case reports. *Acta Pathol Microbiol Scand Sect A* 1977; **85**: 640–8.
- 17 Antine BE, Brown FM, Arisco MJ. Fibroma of the cornea: report of a case associated with congenital generalized fibromatosis. *Arch Ophthalmol* 1974; **91**: 278–80.
- 18 Nasr AM, Blodi FC, Lindahl S, Jinkins J. Congenital generalized multicentric myofibromatosis with orbital involvement. *Am J Ophthalmol* 1986; **102**: 779–87.
- 19 Reese AB. *Tumors of the eye*. 3rd ed. New York: Harper and Row, 1976; 315–6.
- 20 Reich RH. Die lokalisierte kongenitale Fibromatose—ein Beitrag zur differentialdiagnose maligner Tumoren im Kindesalter. *Dtsch Zahnärztl Z* 1981; **36**: 729–31.
- 21 Shnitka TK, Asp DM, Horner RH. Congenital generalized fibromatosis. *Cancer* 1958; **11**: 627–39.
- 22 Stout AP. The fibromatoses. *Clin Orthop* 1961; **19**: 11–7.
- 23 Richardson WR, Dewar JP. Problems in managing fibrous tissue tumors in infants and children. *Surgery* 1964; **56**: 426–36.
- 24 Bartlett RC, Otis RD, Laakso AO. Multiple congenital neoplasms of soft tissues. Report of 4 cases in 1 family. *Cancer* 1961; **14**: 913–20.
- 25 Silberstein MJ, Brodeur AE, Graviss ER, Sundaram M. Diagnosis: congenital generalized fibromatosis. *Orthopedics* 1983; **6**: 456–70.

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Ablepharon macrostomia syndrome

N J Price, R E Pugh, P A Farndon, H E Willshaw

Abstract

The association of congenital ablepharon with the absence of eyelashes and eyebrows, a wide mouth (macrostomia), and auricular, nasal, genital, and other systemic anomalies has been termed the ablepharon macrostomia syndrome. One such case is reported which illustrates the importance of immediate post-natal ocular management to minimise severe visual loss.

Various rare congenital anomalies of the eyelids are known to be associated with other developmental defects. In the ablepharon macrostomia syndrome (AMS) complete absence of all eyelids, a large mouth, absence of eyebrows and eyelashes, low set abnormal pinnae, irregular anterior nares, flattened malar eminences, dry, coarse and redundant skin, absence of lanugo, webbed fingers, absent or vestigial nipples, ambiguous genitalia, cryptorchidism, and ventral hernia may be found.

We believe only three cases of AMS have been reported, the first two by McCarthy and West¹ and a third by Hornblass and Reifler.² We report a further case highlighting the need for urgent eyelid construction.

Case report

The baby was born in July 1986 to a primigravida mother aged 28 years and non-consanguineous father aged 35 years. There was no family history of congenital abnormalities. Pregnancy had been uncomplicated. The following congenital abnormalities were noted at birth; shallow orbits with inadequate eyelids (Fig 1), hypertelorism, large square mouth (Fig 2), protrusion of maxilla, and malformed and low set ears. The skin was wrinkled and hairless; lashes and eyebrows were absent. The genitalia were ambiguous.

Haematological, biochemical, and hormonal profiles and CT scan of the head were all reported as normal. Chromosomal analysis revealed a normal male karyotype.

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Accepted for publication 26 October 1990



Figure 1 Facial appearance at birth. Ablepharon, the absence of all eyelids, with conjunctival chemosis and corneal ulceration.

On the first postnatal day corneal opacities and gross conjunctival chemosis were noted. By the fourth day bilateral corneal vascularisation and central ulcers had developed. Following intensive topical antibiotics and lubricants, bilateral 'tarsorrhaphies' were attempted but had broken down within two days. On the tenth day corneal cover was achieved by supplementing the upper eyelids with bilobed temporal scalp rotation flaps (Fig 3). By age 7 weeks the corneal ulcers had healed, leaving vascularised central opacities. The lids were functioning well. No



Figure 2 Macrostomia, large square mouth with apparent failure of fusion of the lateral lip clefts.



Figure 3 Improved corneal cover and cosmetic appearance following bilateral bilobed temporal scalp rotation flaps.

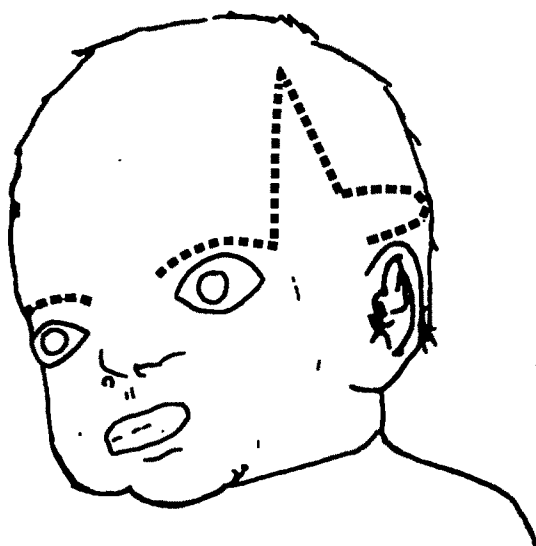


Figure 4 Initial incisions. Bipedicule flaps slide down to form upper lids while rotation flaps fill the resultant defects.

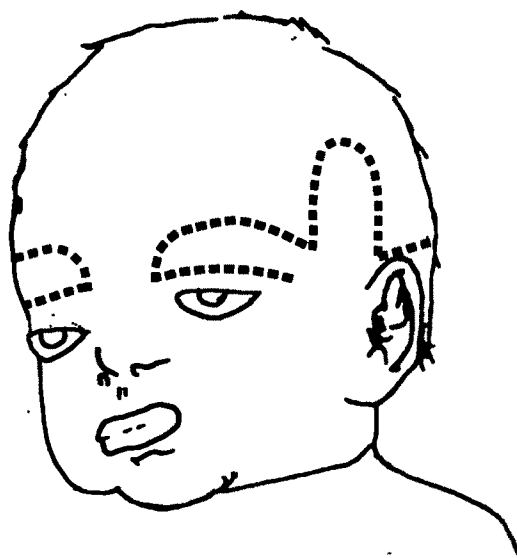


Figure 5 Creation of upper lids following transposition of bilobed rotation flaps.

fundal details could be seen. The flash visually evoked response showed a small P2 and large amplitude P3 at 250 ms. The electroretinogram was normal. His general development at age 15 months was within normal limits for a partially sighted child.

Topical therapy was gradually reduced to liquid paraffin ointment once daily, and by the age of 20 months the corneal opacities had diminished and forced eye closure was complete on both sides. Aged 27 months he underwent right penetrating keratoplasty and bilateral supplementation of the lateral lid regions by means of C-shaped free grafts from the supraclavicular fossae. This improved lid function, cosmetic appearance, and vision. Left penetrating keratoplasty is also planned.

Discussion

This case and the three cases of AMS reported previously by McCarthy and West¹ and by Hornblass and Reifler² share features which characterise a distinct condition. All cases show bilateral absence of eyelids, eyebrows, and eyelashes, an apparent failure of lateral lip fusion giving rise to the large fish-like mouth, abnormal ears and nose, ventral hernia, absence of lanugo, ambiguous genitalia, and cryptorchidism.

In contrast, a female case described by Barber *et al*³ had a remarkably similar facial appearance to the reported cases of AMS but there were other notable differences.³ Cesarino *et al*⁴ chose to describe their case as lid agenesis-macrostromia-psychomotor retardation-forehead hypertrichosis because a number of features differed from those in AMS.

It had been suggested that AMS is an autosomal recessive condition,⁵ as ablepharon may occur in association with cryptophthalmos,^{6,8} which shares many similar systemic features with AMS.^{6,9-11} However, in AMS the periorbital tissues are not fused with the ocular surface, all cases appear to be sporadic, and all chromosomal studies have shown a normal male karyotype.

The ophthalmic management of these neonates begins at birth, with frequent instillation of ocular lubricants and antibiotics. Moisture

chambers with plastic wrappings⁷ or even inferior rectus section with upward rotation of the globe¹² may help as temporary measures.

Most techniques described for four-lid construction in the adult involve stages in which total visual occlusion occurs for some weeks,¹²⁻¹⁵ which in the neonate could induce amblyopia. In our case, once tarsorrhaphies had failed, the upper eyelids were lengthened by making horizontal relieving incisions down to the levators and sliding them down as bipedicule flaps. The defects were filled by means of bilobed transposition flaps from the temporal scalp on either side (Figs 4, 5). The flaps are formed at right angles to each other and then transposed round into the defect. The resultant defect in the first axis is then closed.¹⁶ There was sufficient conjunctiva present to obviate the need for mucosal grafts. This technique was favoured because it utilised the excessive and hairless temporal scalp skin¹⁷ and the preseptal orbicularis muscle was retained at the lid margin.

Postulated mechanisms for AMS are a primary developmental failure, a destruction/absorption process, or some mechanical interference. These would not, however, explain the other associated abnormalities. Neural crest-derived cells contribute to the connective tissue of the eyelids.¹⁸ An ectodermal-mesenchymal induction failure could result in ablepharon and the other manifestations of AMS. The thin dry skin lacking in subcutaneous tissue may indicate a primary skin disorder. Perhaps a defect in skin elastic tissue and therefore skin tension during development results in the observed abnormalities (Donnai D, personal communication, 1986). Thus the eyelids may have been prevented from fusing and thereby completing normal development. There are no reports on skin histology in AMS, but periorbital skin biopsies from our case showed no specific abnormality, and collagen studies gave normal findings.

We thank especially Mr L A Holbrook, of Alder Hey Hospital, Liverpool, for performing the plastic surgery, Dr Michael Pope, of Northwick Park Hospital, for the collagen studies, and the Departments of Medical Illustration at Leighton Hospital, Crewe; Selly Oak Hospital, Birmingham and the Royal Hospital, Wolverhampton, for the illustration.

- 1 McCarthy GT, West CM. Ablepharon macrostomia syndrome. *Dev Med Child Neurol* 1977; **19**: 659-72.
- 2 Hornblass A, Reifler DM. Ablepharon macrostomia syndrome. *Am J Ophthalmol* 1985; **99**: 552-6.
- 3 Barber N, Say B, Bell RF, Merveille OC. Macrostomia, ectropion, atrophic skin, hypertrichosis and growth retardation: case report 83. *Syndr Indent* 1982; **8**: 6-9.
- 4 Cesarino EJ, Pinheiro M, Freire-Maia N, Meira-Silva MC. Lid agenesis-macrostromia-psychomotor retardation-forehead hypertrichosis: a new syndrome? *Am J Med Genet* 1988; **31**: 299-304.
- 5 Gupta SP, Saxena RC. Cryptophthalmos. *Br J Ophthalmol* 1962; **46**: 629-32.
- 6 François J. Malformative syndrome with cryptophthalmia. *Int Ophthalmol Clin* 1968; **8**: 817.
- 7 Azevedo ES, Biondi J, Ramalho LM. Cryptophthalmos in two families from Bahia, Brazil. *Braz J Med Genet* 1973; **10**: 389-92.
- 8 Sugar HS. The cryptophthalmos-syndactyly syndrome. *Am J Ophthalmol* 1968; **66**: 897-9.
- 9 Zehender W, Manz O. Eine Missgeburt mit hautüber wachsenen Augen oder Kryptophthalmus. *Klin Monatsbl Augenheilkd* 1872; **10**: 225-49.
- 10 Fraser GR. Our genetic 'load'. A review of some aspects of genetic variation. *Ann Hum Genet* 1962; **25**: 387-415.
- 11 Ide CH, Wollschlaeger PB. Multiple congenital abnormalities associated with cryptophthalmia. *Arch Ophthalmol* 1969; **81**: 638-44.
- 12 Tessier P. Secondary treatment of the injured and mutilated eyelid. In: Tessier P, Callahan A, Mustardé JC, Salyer KE, eds. Symposium on plastic surgery in the orbital region. *Proceedings of the symposium of the Educational Foundation of the American Society of Plastic and Reconstructive Surgeons, Inc.* St Louis: Mosby, 1976; **12**: 55.
- 13 Mustardé JC. Reconstruction of both lids. In: Mustardé JC. *Repair and reconstruction in the orbital region. A practical guide.* 2nd ed. London: Churchill Livingstone, 1980: 152-4.
- 14 Hay D. Reconstruction of both eyelids following traumatic loss. *Br J Plast Surg* 1971; **24**: 361-4.
- 15 Achauer BM, Menick FJ. Salvage of seeing eyes after avulsion of upper and lower lids. *Plast Reconstr Surg* 1985; **75**: 11-5.
- 16 Dean RK, Kelleher JC, Sullivan JG, Baibak GJ. Bilobed Flaps. In: Grabb WC, Myers MB, eds. *Skin flaps.* 1st ed. Boston: Little, Brown, 1975: 289-96.
- 17 Esser JFS. Gestielte lokale Nasenplastik mit Zweizipfligen Lappen, Deckung des sekundären Defektes vom ersten Zipfel durch den Zweiten. *Dtsch Z Chir* 1918; **143**: 385.
- 18 Noden DM. Periocular mesenchyme, neural crest and mesodermal interactions. In: Duane TD, Jaeger EA, eds. *Biomedical foundations of Ophthalmology.* Philadelphia: Harper and Row, 1982: **1**: chapter 3: 14.

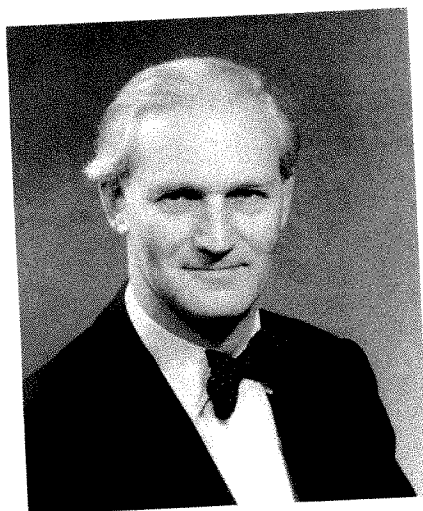
OBITUARY

HE Hobbs, MB, BS, FRCS, DOMS, DO

Henry Edwin Hobbs died on 3 October 1990 after a long illness.

His career spanned a period when the practice of ophthalmic surgery finally emerged from being the part-time preoccupation of a general surgeon with a particular interest into a specialty in its own right. Indeed his own interest in ophthalmology appears to have arisen during his short period as an optician and his resolve to move into a medical career must have demonstrated itself to the London Hospital Medical School, doubtless impressed by the self-discipline he had shown in holding down a job in optical manufacturing while educating himself to university entrance standard at night school.

After qualification in 1938 with some distinction in his undergraduate career, he did house jobs, then took the FRCS in 1941, proceeding to the DOMS and the Oxford DO in 1942, and entered the Royal Air Force as an ophthalmic specialist with the rank of squadron leader. After the war he was swept along in the sea change taking place which made ophthalmology a scientific discipline. He was particularly to the fore in advances in glaucoma, and some of those who have become acknowledged experts in this field are indebted to him for stimulating their initial interest in the subject.



Glaucoma work inevitably involved study of visual field anomalies, which served him well in his subsequent appointment to the Maida Vale Branch of the National Hospital, where he developed a useful device for fixation of an eye with a central scotoma during Bjerrum screen examination. He was registrar (a title of some greater significance in those days) and chief assistant at the Holborn Branch of Moorfields before taking up consultant posts first at the Metropolitan Hospital and subsequently at the Royal Northern and Royal Free Hospitals. In his later career he retained his Royal Free and Maida Vale appointments as well as his busy private practice. He was highly respected by all his patients, and his work often extended beyond the merely clinical. The Royal Free benefited from this when Henry was secretary of the medical committee; he organised very

successful annual staff dinners at Claridges through just such a 'patient connection.'

Apart from his early glaucoma work he will certainly be best remembered for the original observation of chloroquine retinopathy documented in the joint paper written by him with Sorsby and Freedman and published in the *Lancet* in 1959. He came from a deeply religious background, which may have prompted his ophthalmological concern for leprosy sufferers: he was honorary consultant ophthalmic surgeon to the Hospital and Homes of St Giles, East Hanningfield. Leprosy work was regarded as particularly important to the Hospital of St John of Jerusalem. In recognition of this and other Christian acts he was appointed first an officer and subsequently, in 1970, a commander of the Order of St John.

Once he retired from active practice he moved permanently to the country, where he was able to pursue even more assiduously his life-long interests in music and, after a successful hip replacement, gardening. Sadly, his wife died not long after he retired, but his independence carried him through for some years until he became unwell. And he was without doubt sustained by his three daughters, all of whom were a great source of pride. To those of us who had close professional contact with him he will be best remembered for his valued clinical opinion, delivered diffidently but directly, a meticulous surgeon, and as a colleague whose fairness and rectitude characterised his personal relationships.

DAVID ABRAMS

LETTER TO THE EDITOR

Macular degeneration: the facts

SIR,—Most scientific papers dealing with macular degeneration begin with the following type of statement: 'Macular degeneration . . . is the leading cause of severe visual loss in the United States and western Europe in persons aged 55 years or older . . . [it] is of unknown cause.'

Even the public understands the problem: 'After AIDS and cancer, the medical crisis Americans fear most is blindness. . . . More than half of all Americans with low vision have macular degeneration, a deterioration, of the retina that is the number one cause of visual deficiency in the elderly. . . . Although help for low-vision is plentiful, ophthalmologists often fail to refer patients to low-vision organisations. . . .'

'I can't stand the fact that many of my colleagues abrogate their responsibility,' says Dr Eleanor E Faye, who was a pioneer in developing low vision as a clinical specialty. 'No orthopedist would tell a patient, 'Well the bone is knit and your arm is bent at a 45-degree angle, but there's nothing more I can do for you' (personal communication).

There appears to be only a low correlation between the number and quality of publications (though there is no question that if there were no reports there could not be any quality). To examine this issue we studied the number of publications dealing with macular degeneration as reported in one of our leading medical listing services (*Index Medicus*). Our records show that 609 articles appeared during the last

decade, of which 202 were in foreign languages (and therefore not readily available for study). With regard to causation, the annual average in English language journals is two to four. In all, we found 38 over the past 10 years.

It is obvious from this search of the literature that very little effort has been expended to determine the cause of macular degeneration. To put this into proper perspective, during the same period, 320 articles appeared in 1983 on the subject of AIDS. This has exploded to approximately 6000 in 1989 even though the incidence and prevalence as well as the devastation of AIDS and macular degeneration are comparable.

Therefore one must wonder whether we are dealing here with a truly insolvable problem, or whether, if greater and more organised effort were to be expended, the problems of macular degeneration might be solved.

E CHERASKIN
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School of Medicine,
Birmingham, Alabama 35294, USA

- 1 Newsome DA, Swartz M, Leone N, Elston R, Miller E. Oral zinc in macular degeneration. *Arch Ophthalmol* 1989; **106**: 192-8.
- 2 Seligmann J. Making the most of sight: a brighter future for the millions of Americans with 'low' vision. *Newsweek* 92-93, 16 April 1990.

NOTES

Research grants

David Cole travel fellowship

The David Cole travel fellowship, instituted by Merck Sharp and Dohme in memory of Professor David Cole, will assist a visit to hospital or research centre during the academic year starting 1 October 1991. The award will be equivalent to £2000. The purpose of the award is to enable the successful applicant to gain experience and knowledge in pursuit of specific project related to glaucoma.

Glaucoma Group research grant

The Glaucoma Group research grant, sponsored by the International Glaucoma Association, will be available for a research project clinically orientated to glaucoma for 1991. The award will be equivalent to £2500. The grant may be used towards salary or project expenses or for buying equipment.

Glaucoma Group research award

The Glaucoma Group research award, sponsored by Alcon Laboratories, will be given in support of a research project related to glaucoma. The award will be equivalent to £2000.

These awards are available to both medical graduates and non-medical scientists residing in the United Kingdom or Irish Republic. They may be held concurrently with other awards. Further details and application forms from: Dr S Nagasubramanian, Secretary of Glaucoma Group, Glaucoma Unit, Moorfields Hospital, City Road, London EC1 2PD. The closing date for applications is 30 June 1991. The successful candidates will be informed August 1991.

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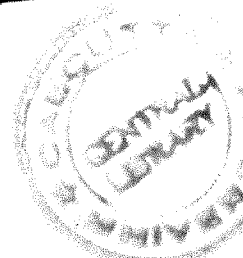
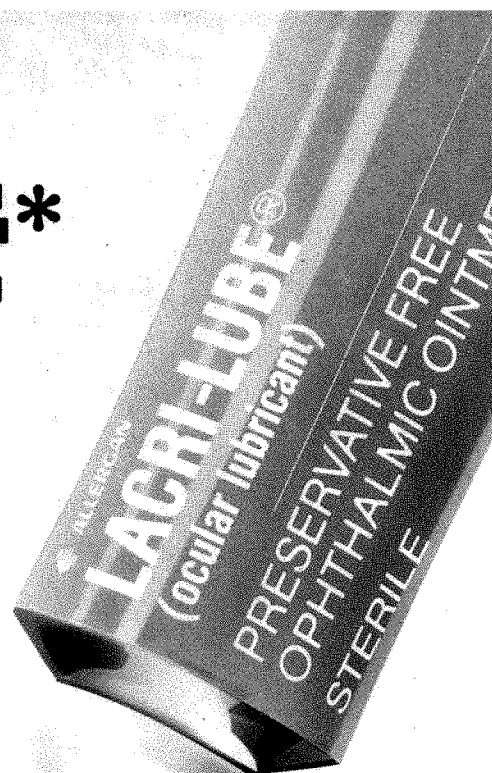
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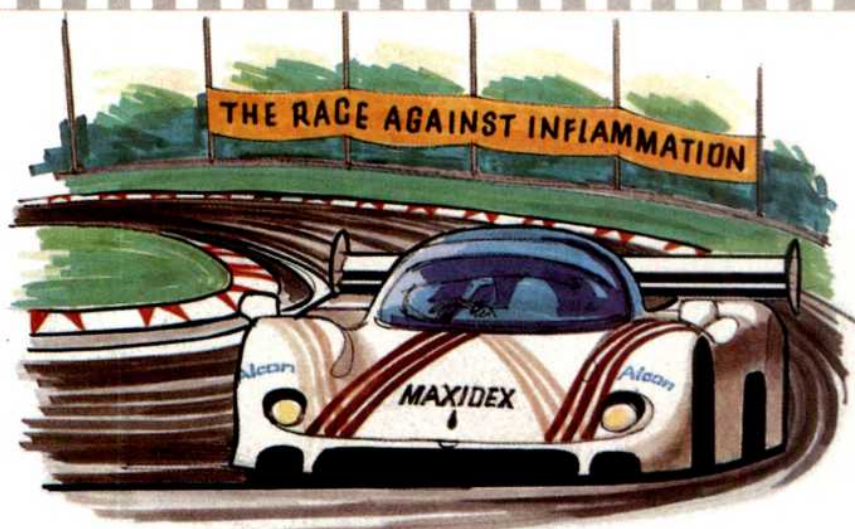
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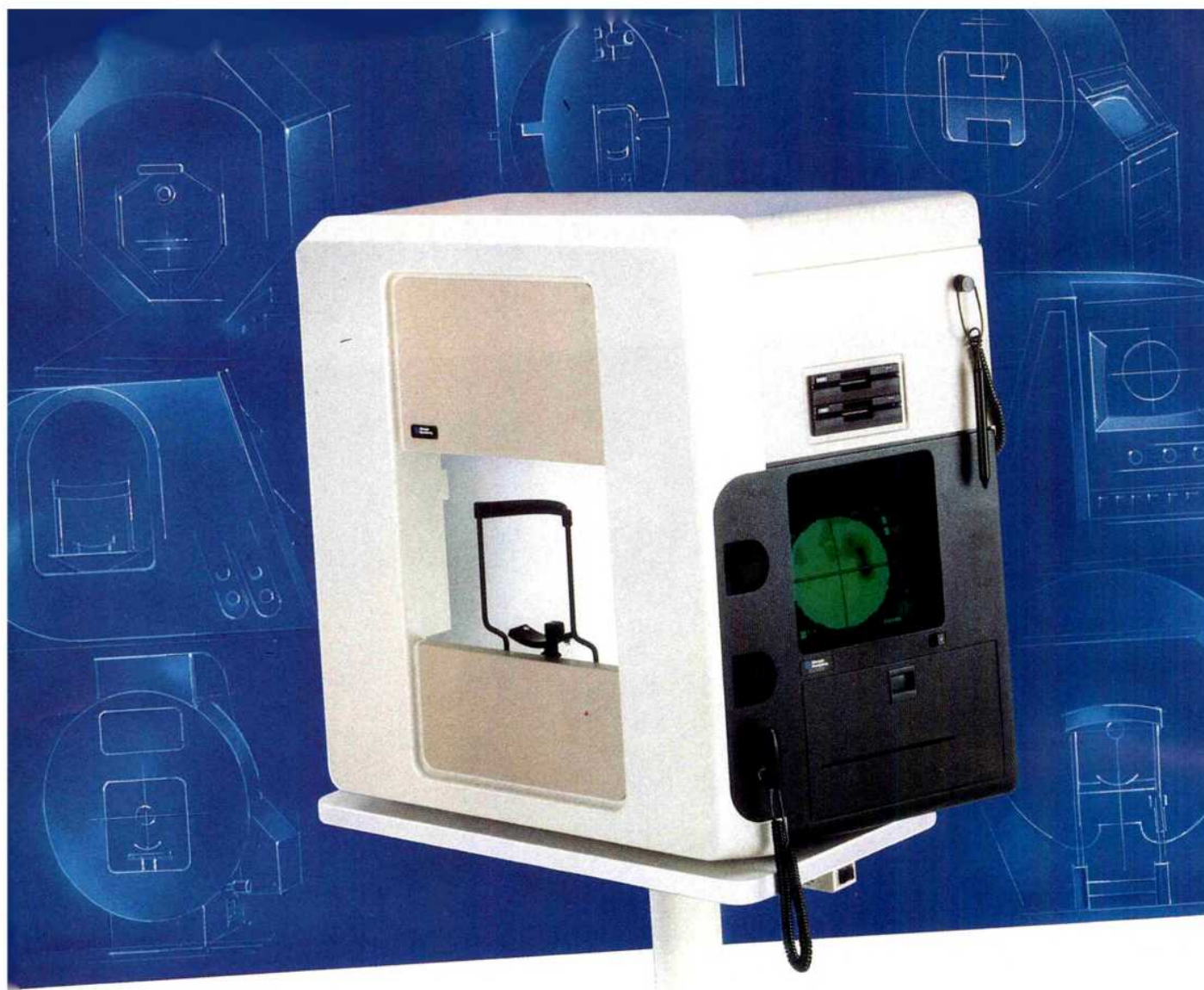
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BRITISH JOURNAL OF OPHTHALMOLOGY

Editorial

Trachoma still undefeated

An attempt to cover the literature on trachoma for the purpose of writing an editorial note brings home to one its immensity and variety, dealing as it does not only with the clinical, epidemiological, and surgical but also the public health aspects of the disease, as in the paper by Courtwright and others in this issue. Furthermore trachoma has a rich historical literature, admirably summarised by Duke-Elder,¹ in which he reminds us among other things of the ancient records of trachoma from China in the 27th, Sumeria in Mesopotamia in the 20th, and Ancient Egypt in the 19th centuries BC. It also appears in the literature of Greece and ancient Rome, and according to Duke-Elder the name trachoma was used by a Cilician physician, Pedanius Dioscorides, in the first century AD. An English translation of trachoma, which is derived from the Greek meaning rough, is granular conjunctivitis, and one remembers that, if the conjunctiva was thought to be rough, the treatment was even rougher, for the 'granulations' (follicles) were drastically dealt with by scraping, rolling, mangling, and gouging with a selection of ferocious instruments in combination with the stringent application of various caustic agents.

The paper in this issue is a salutary reminder to ophthalmologists from the developed countries, who tend to be inundated with 'high tech' literature, not to forget trachoma. During the 90 years of the present century there have been at least a dozen major textbooks on the subject and during the last 40 years alone several thousand papers and monographs, though it is noticeable that the number per annum has declined in the last few years from well over 100 in the 1950s and 1960s to rather fewer in the last two or three years.

These papers cover such diverse and curious aspects as the development of immunity to chlamydia in monkeys,² the use of trachoma to avoid military service,³ daily treatment of the lids with tannic acid⁴ or amnion grafts,⁵ 'moss' (fungi imperfecti) as a suggested aetiological agent,⁶ and a cure by homeopathy⁷ as well as a mass of serious accounts of aetiology, pathology, and treatment both medical and surgical, together with an exhaustive list of surveys in virtually every part of the world, from Austria to Vietnam, from Casablanca to China, from France to Fiji, and from South Africa to Serbia to name but a few.

As one traces the development of our understanding of the disease, it is interesting to see the gradual dawning of understanding of the presumed aetiological agent with its variable expression as sometimes relatively mild 'inclusion conjunctivitis' or the severe form of trachoma. The cause of such diverse manifestations of the response to the *Chlamydia trachomatis* as occur clinically has always been difficult to explain.

It is interesting that in 1970 Wang and Grayston⁸ suggested that differences in the host immunological status could cause differing clinical syndromes in infection by similar organisms, and it was from such immunological studies that the serotyping of the virus soon evolved. That the organism

C. trachomatis is the essential infective agent seems now to be universally agreed, though since the original description of inclusion bodies by Halberstaedter and Prowazek in 1907⁹ there has been some uncertainty about the exact role of these bodies. The position has now been consolidated by the work of T'ang and coworkers,¹⁰ who cultivated the virus on chick embryo. Further, Thygeson suggested the agent's inclusion in a list of 'atypical viruses' of the psittacosis-lymphogranuloma-venereum group under the generic name of Chlamydozaceae.¹¹ Trachoma and inclusion conjunctivitis were attributed to different members of the group, though for some years others thought that there was only a single agent, so that the differing manifestations gave rise to a certain amount of confusion. The identification of distinct serotypes characteristic either of hyperendemic blinding trachoma of eye-to-eye transmission or the much less menacing paratrachoma, typically sexually or perinatally acquired, has confirmed Thygeson's prediction and eliminated the confusion. An excellent summary of the refinement of our understanding of the infective agent has been given by Barrie Jones,¹² who with his coworkers has done a great deal to identify the points of similarity and difference between blinding trachoma and inclusion conjunctivitis by means of both epidemiological and laboratory investigations.

Much present research is now concerned with the application of our better understanding of the nature of the infective agent and its modes of transmission. The various risk factors and their roles in relation to local geography and politics in various parts of the world are being widely examined, such things as water supply, sewage disposal, fly control, and traditions of and facilities for personal hygiene probably being equally if not more important than the availability of local or even systemic antibiotics. It is clear that along with cataract, nutritional deficiencies, and onchocerciasis trachoma is still one of the world's major blinding diseases.

REDMOND SMITH

- 1 Duke-Elder WS. *System of ophthalmology*. London: Kimpton, 1965; 7 (1): 249-303.
- 2 Taylor HR. Development of immunity to ocular chlamydial infection. *Am J Trop Med Hyg* 1990; 42: 358-64.
- 3 Lopez AA. Trachoma and military service. *Arch Soc Oftalmol Hispano-Am* 1949; 9: 1102-6.
- 4 Pavkovic-Bugarski D. Treatment of trachomatous pannus with amnion grafts. *Srp Arh Celok Lek* 1950; 48: 866-8.
- 5 Sedan J, Sedan-Bauby S. The daily treatment of trachoma by tannic acid. *Rev Int Trach Pathol Ocul Trop Sante Publique* 1949; 26: 177-84.
- 6 Socias A. The hypothesis of a fungal aetiology of trachoma. *Rev Sanid Hig Publica (Madrid)* 1950; 24: 422-43.
- 7 Apte GD. Homeopathy and ophthalmic practice. *Indian J Ophthalmol* 1951; 12: 65-8.
- 8 Wang S, Grayston JT. Immunologic relationship between genital TRIC, lymphogranuloma venereum, and related organisms in a new microtiter indirect immunofluorescence test. *Am J Ophthalmol* 1970; 70: 367-74.
- 9 Halberstaedter L, von Prowazek S. Über zillenschlüsse parasitäre Natur beim Trachome. *Arch K Gesundheitsamte (Berlin)* 1907; 26: 44-7.
- 10 T'ang FF, Huang YT, Chang HL, Wang KC. Isolation of trachoma virus in chick embryo. *J Hyg Epidemiol Microbiol Immunol* 1957; 1: 109-20.
- 11 Thygeson P. The trachoma-psittacosis-lymphogranuloma venereum group of viruses: the chlamydozaceae. *Am J Ophthalmol* 1951; 34: 7-34.
- 12 Jones BR. The prevention of blindness from trachoma. *Trans Ophthalmol Soc UK* 1975; 95: 16-33.

ORIGINAL ARTICLES

Latrine ownership as a protective factor in inflammatory trachoma in Egypt

Paul Courtright, John Sheppard, Sandra Lane, Aly Sadek, Julius Schachter, Chandler R Dawson

Abstract

We investigated the association between inflammatory trachoma in children aged 1-5 and environmental and sociodemographic risk factors in a rural Nile Delta hamlet. Inflammatory trachoma clustered in households, emphasising the child-to-child nature of transmission in the hamlet. Multiple logistic regression analysis revealed three factors predicting inflammatory trachoma in children: the absence of a latrine in the household, school-age siblings with inflammatory trachoma, and additional same-age siblings (with or without disease) in the household. In the Egyptian setting the presence of pit latrines in all houses, even when full and unscreened, might result in a reduction in trachoma prevalence in this population from the current 49% to 35%. The construction of pit latrines may offer the simplest and most acceptable environmental method for reducing trachoma in this trachoma endemic area.

Much progress has been made recently in elucidating the factors, some of which may be cultural or site specific, influencing the intensity of inflammatory trachoma in children. However, all the factors associated with inflammatory trachoma which might be amenable to intervention have not been established. As with other communicable diseases, trachoma is intricately bound up with environmental, demographic, and social factors. Poor hygiene (including face washing) and low socioeconomic status are most commonly cited as risk factors for the presence of inflammatory trachoma.¹⁻¹⁸ Researchers have identified other risk factors for trachoma inflammation including fly density,¹⁹⁻²⁰ geographic and climatic characteristics,²¹⁻²² crowding and family size,²³⁻²⁵ and occupation and education of household head.²³⁻²⁵ There is considerable intercorrelation between these predictors of trachoma inflammation, and yet in only three of these studies¹⁻¹⁸ were the predictors assessed independently. Furthermore, the contribution of household clustering of trachoma to the results was not examined.

The purpose of this study was to define those environmental characteristics that were independently associated with inflammatory trachoma in the rural Nile Delta of Egypt and to suggest public health measures to reduce the prevalence of trachoma.

Materials and methods

All residents of an Egyptian Nile Delta hamlet, Kafr (population 1107), were examined with a portable slit-lamp for inflammatory and cicatricial trachoma in January 1987. This area has been the focus of considerable population based research into blindness and trachoma because trachoma remains a serious public health problem.²⁶⁻²⁹

The clinical findings were recorded by the detailed WHO grading system for trachoma.³⁰ For the purpose of this paper inflammatory trachoma was recorded as present if the inflammatory disease was of moderate to severe intensity, and absent if there was mild to insignificant conjunctival inflammation. Trachoma intensity was determined by the disease in the worse eye. The analysis focuses on children aged 1-5 years, because this age group accounts for the bulk of the inflammatory trachoma in this and other trachoma endemic populations. Furthermore, the environment of children aged 1-5 is closely linked to the household, the focus of this risk factor investigation, while children older than 5 have substantial contact outside the

Table 1 Environmental and socio-demographic factors investigated in Kafr, Egypt, 1987

TV ownership
Radio ownership
Car ownership
Fedan (acreage) usage
Farm animals
Buffalo
Cattle
Donkey
Goats and sheep
Chickens
Wall type (mud brick, stone, brick)
Floor type
Presence of latrine
Number of rooms
Number of sleeping rooms
Education of household head
Education of other men in household
Education of women
Education of school-age boys
Education of school-age girls
Occupation of household head
Occupation of other men in household
Number of adults
Number of schoolage youths (aged 6-14)
Number of children (aged 1-5)
Disease in school age youths
Age
Sex
Age of household head
Average age of household members
Residence of family in 1972
in hamlet, same location
in hamlet, different location
outside hamlet

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Department of Community Medicine, University of Alexandria, Egypt
A Sadek

Correspondence to: Dr P Courtright, PO Box 2273, Blantyre, Malawi.
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Accepted for publication 13 November 1990

household. Children less than 1 year old were excluded from the data set owing to the difficulty of examining infants and the low prevalence of clinical disease in this age group.

A household was defined as the aggregate of persons who, at the time of the survey, were sleeping in the same house. Thus households generally consisted of extended families and, in rare cases, persons not related by kinship to the head of the household.

Data on environmental and socio-demographic factors, shown in Table 1, were collected on both the household (cluster) level and individual level by interview and observation. Constructed variables included number of persons per sleeping room and number of large farm animals per person per room. The former is a measure of the potential for transmission of trachoma, and the latter (animal are kept in the house) is a measure of socioeconomic status and exposure to animal wastes.

We assessed the interrelation between risk factors and their effect on trachoma status by multiple logistic regression analysis using EGRET, controlling for other confounding variables and the contribution of household clustering in the results.³¹ A subset of variables representing potential predictors of trachoma by univariate analysis (χ^2 exceeding 2.4, or $p < 0.11$) were selected for inclusion in the logistic model. Variables were included in the regression model on a step-wise fashion to construct an estimate utilising information from the other factors to estimate the risk in each one, giving rise to the odds ratio as a measure of association. Although not presented here, the role of household clustering on the results was assessed to ensure the validity of the results.³²

Results

We examined 225 of 232 children aged 1–5 (response rate = 97%) from 96 households. The prevalence of inflammatory trachoma (severe and moderate intensity) in the study population was 49%. The age specific prevalence of active inflammation peaked at 60% among children 3 years old, and boys had a slightly higher prevalence of active trachoma than did girls (Table 2).

There was a strong tendency for trachoma to cluster in households. In 13 of 66 households (20%) with two or more children there were no active trachoma cases, while in 21 of the remaining households (32%) all children in the target age group had active trachoma. Household clustering of trachoma, while significant in nature, did not change the relative significance of the findings.

There is no running water or electricity in the hamlet, and only two vehicles are owned by residents. Homes are tightly packed in a half-square mile (1.3 km²) area, and there are large piles of manure (human and animal) throughout the hamlet. All residents are Muslim and most are long-term inhabitants. Televisions and radios are operated on automobile batteries. Most families (53%) reported that they farmed two fedan – about 1.5 acre (0.6 ha). Twenty-eight households (22%) did not engage in farming.

The majority of houses were constructed from packed mud, but newer houses have been constructed from either stone or brick. Just under half of the houses had a pit latrine; the rest had no latrine. The median number of rooms per household was four, with a range of one to 10. Young children slept together with their parents in one large bed, and older siblings, particularly boys, often slept with grandparents in a separate room. Only 21% of households did not own a donkey, while 13% owned two or more. Many men worked in a textile mill 10 km distant. Only 22% of girls of school age attended school.

Univariate analysis of data according to the trachoma status of the household is given in Table 3. Utilising multiple logistic regression analysis we concluded that the number of children in the household, the absence of a latrine in the household, and disease in school-age siblings were the most important factors associated with trachoma intensity in children (Table 4). Other variables failed to explain

Table 2 Prevalence of inflammatory trachoma by age of children in Kafr, Egypt, 1987

Age (years)	Severe/moderate trachoma (%)	No trachoma (%)
1	16 (42%)	22 (58%)
2	23 (50%)	23 (50%)
3	29 (60%)	19 (40%)
4	23 (50%)	23 (50%)
5	20 (43%)	27 (57%)
Total	111 (49%)	114 (51%)

Table 3 Distribution of household characteristics

Characteristic	Trachomatous household*	Non-trachomatous household
TV/radio ownership		
Both owned	19 (20%)	21 (22%)
Neither/either	36 (38%)	18 (19%)
People per fedan	5.98	4.82
Number of animals	3.68	2.67
Animals per room	0.80	0.57
Latrine in house		
Absent	37 (39%)	13 (14%)
Present	18 (19%)	26 (27%)
Rooms per person	2.92	2.27
Occupation of males		
Farmer/manual labor	40 (43%)	25 (26%)
Factory/professional	15 (16%)	14 (15%)
Trachoma in school age siblings		
Present	30 (32%)	9 (10%)
Absent	25 (26%)	30 (32%)
Number of children 1–5	2.85	2.00
Number of youths 6–14	2.69	1.92
Number of adults 15+	5.60	4.33

*Trachomatous household defined as household with at least one child (age 1–5) with moderate-severe inflammatory trachoma. 1 Fedan = 0.3 ha.

Table 4 Predictors of disease: odds ratio (and confidence intervals) in Kafr, Egypt, 1987

Parameter	Odds ratio (95% CI) p
Disease in school-age siblings	4.4 (2.0, 10.8) <0.001
Absence of latrine	3.3 (1.6, 6.2) <0.001
Number of children	1.3 (1.2, 1.5) 0.01

Table 5 Proportion of children aged 1–5 by size of household

Household size*	Children as percentage of total household members
1–4 members	15%
5–8 members	20%
9–12 members	20%
13+ members	24%

Test for trend: $F = 14.0$, $p < 0.001$.

*Number of inhabitants sleeping in the same household.

independently the variation in trachoma intensity in this population. The presence of a latrine was not associated with various measures of socio-economic status, including occupation and education of household head, number of large farm animals, and acreage farmed by the household.

The number of children (aged 1-5) in households ranges from 0 to 12 with a median of 2. Households with numerous members had proportionately more children than households with few members (Table 5). The log odds of disease in a child increased by 0.22 with each additional same-age sibling. Thus the odds of disease in a child with one same-age sibling was 1.3, and for a child with three same-age siblings it was 1.9 ($p=0.01$). Among households with numerous children there were no differences in rates of active trachoma for those with fewer sleeping rooms than those with numerous sleeping rooms.

Independently of the number of children in the household the presence of trachoma in school-age siblings aged 6-14 was associated with inflammatory trachoma in children aged 1-5. The prevalence of trachoma in preschool children in the 15 households that had no school-age sibling was 36%, the same as the prevalence in the 54 households with non-trachomatous school-age siblings (37%). By comparison there was a high prevalence (78%) of trachoma in preschool children in the 25 households with a trachomatous school-age sibling. Nevertheless, only 50% of diseased children had a trachomatous school-age sibling. This suggests that trachoma is more probably transmitted between younger children than from school-age youths to their younger siblings.

Discussion

Trachoma remains a serious public health problem among rural inhabitants in the Egyptian Nile Delta. The high correlation between trachoma status of children in the same household probably reflects both the infectious nature of trachoma and the strong dependence of intensity of inflammatory disease on environmental and socio-demographic factors common to the household. Thus the detection of household clustering of trachoma is fundamental in trying to explain trachoma distribution in a population and in understanding the risk factors for disease.

From a public health standpoint the reduction in the number of young children in the household is not a realistic measure. While there is a nationwide family planning programme in Egypt, a number of factors have limited the effectiveness and use of family planning in rural hamlets. Child spacing is rarely practised, and contraceptives are not used. Consequently, women bear children throughout their child-bearing years. In the recent past maternal and child care has improved, with the result that infant mortality is only 85/1000 live births and life expectancy at birth is about 60 years.³³ Because of increased child survival, households in Kafr were larger in 1987 (median = 8) than in 1972 (median = 6). On the other hand new houses are continually under construction in the

hamlet, and single-family dwellings are becoming more common than extended-family dwellings. Effective population control is likely to reduce the amount of trachoma as well as other infectious diseases endemic to this region.

At first glance it may appear that the identification of trachomatous school children is a simple alternative to population based surveys to identify trachoma in preschool children or trachomatous households. However, this technique is not sensitive enough to identify these preschool children; only 50% of diseased children are in households with a trachomatous school-age sibling, and not all children attend school.

Latrines in many rural Nile Delta hamlets consist of an unscreened pit, commonly dug 10 to 15 years ago, in one of the rooms of the house. Although families with latrines do not always use them consistently, they still provide a more hygienic situation than the alternative, which is defecation in the common room used as both the kitchen and stable of the house. Small children defecate wherever it suits them inside and outside the house. Faecal matter around the house probably contributes to increased fly density. Fly suppression through application of insecticide has not yielded good enough results to recommend it as a long-term preventive measure of trachoma.³⁴ Fly control, which may be partially achieved through the introduction of screened pit latrines, has been suggested previously, though controlled studies have not been undertaken and the cost and efficacy of achieving it are not clear.^{20,35} Nevertheless in the Egyptian setting the presence of pit latrines in all houses, even when full and unscreened, might result in a reduction in trachoma prevalence in this population from the current 49% to 35%. The construction of latrines should be encouraged to improve general hygiene and reduce trachoma in this region.

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- 1 Tielsch JM, West KP, Katz J, *et al.* The epidemiology of trachoma in southern Malawi. *Am J Trop Med Hyg* 1988; 32: 393-9.
- 2 Sowa S, Sowa J, Collier LH, Blyth A. *Trachoma and allied infections in a Gambian village*. London: Medical Research Council, 1965.
- 3 Taylor HR, Velasco FM, Sommer A. The ecology of trachoma: an epidemiological study in southern Mexico. *Bull WHO* 1985; 63: 559-67.
- 4 Foster SO. Trachoma in an American Indian village. *Public Health Rep* 1965; 80: 827-32.
- 5 Portnoy GL, Portnoy SB. Epidemiology of trachoma in the San Xavier Papago Indians. *Arch Ophthalmol* 1971; 86: 260-2.
- 6 Mathur GM, Sharma R. Prevalence of trachoma and other common eye diseases. *Ind J Med Res* 1970; 58: 1085-99.
- 7 Royal Australian College of Ophthalmologists. *The National Trachoma and Eye Health Programme of the Royal Australian College of Ophthalmologists*. Sydney, 1980.
- 8 Lane SD. A biocultural study of trachoma in an Egyptian hamlet. PhD dissertation. San Francisco: University of California, 1987.
- 9 Parthasarathy NR, Gupta CK. Influence of some of the socio-economic factors in the prevalence of trachoma. *Ind J Social Work* 1962; 23: 127-31.
- 10 Taylor CE, Gulati PV, Harinarain J. Eye infections in a Punjab village. *Am J Trop Med Hyg* 1958; 7: 42-50.
- 11 Brilliant LB, Pokheral RP, Grasset NC, *et al.* Epidemiology of blindness in Nepal. *Bull WHO* 1985; 63: 375-86.
- 12 Gilbert SS. Trachoma in Nepal: an investigation into socio-cultural and individual factors. PhD dissertation. Ann Arbor: University of Michigan, 1983.
- 13 Winkler PF. The morbidity survey on trachoma and other communicable eye diseases in the district of Hebron, Jordan, 1960. *Bull WHO* 1963; 28: 417-36.

- 14 Marshall CL. The relationship between trachoma and piped water in a developing area. *Arch Environ Health* 1968; 17: 215-20.
- 15 Amies CR, Loewenthal LJA, Murray NL, Scott JG. Blindness in the Bantu: a survey of external eye disease and malnutrition in the northeastern Transvaal. *S Afr Med J* 1953; 27: 593-7.
- 16 Kok PW. The epidemiology of trachoma blindness in Southern Africa. *Soc Sci Med* 1983; 17: 1709-13.
- 17 Pratt-Johnson JA, Wessels JHW. Investigation into the control of trachoma in Sedkhukuniland. *S Afr Med J* 1958; 32: 212-5.
- 18 Taylor HR, West SK, Mmbaga BBO, et al. Hygiene factors and increased risk of trachoma in Central Tanzania. *Arch Ophthalmol* 1989; 107: 1821-5.
- 19 de Sole G. Impact of cattle on the prevalence and severity of trachoma. *Br J Ophthalmol* 1987; 71: 873-6.
- 20 Jones BR, Darougar S, Mohsenine H, Poirier RH. Communicable ophthalmia: a blinding scourge of the Middle East. *Br J Ophthalmol* 1976; 60: 492-8.
- 21 Cooper SN. Trachoma: a bio-meteorological approach. *J All-India Ophthalmol Soc* 1964; 12: 50-8.
- 22 Dhir SP, Detels R, Alexander ER. The role of environmental factors in cataract, pterygium and trachoma. *Am J Ophthalmol* 1967; 64: 128-35.
- 23 Bobb AA, Nichols RL. Influence of environment in clinical trachoma in Saudi Arabia. *Am J Ophthalmol* 1969; 67: 235-43.
- 24 Nichols RL, Von Fritzinger K, McComb DE. Epidemiological data derived from immunotyping of 338 trachoma strains isolated from children in Saudi Arabia. In: Nichols RL, ed. *Trachoma and related disorders caused by chlamydial agents*. Excerpta Medica Int Congr Ser No. 223. London: 1971: 337-57.
- 25 Assaad FA, Maxwell-Lyons F, Sundarsen T. Use of local variations in trachoma endemicity in depicting interplay between socio-economic conditions and disease. *Bull WHO* 1969; 41: 181-94.
- 26 Courtright P, Sheppard J, Schachter J, Said ME, Dawson CR. Trachoma and blindness in the Nile Delta: current patterns and projections for the future in the rural Egyptian population. *Br J Ophthalmol* 1989; 73: 535-40.
- 27 Said ME, Goldstein H, Korra A, El-kashlani K. Prevalence and causes of blindness in urban and rural areas of Egypt. *Public Health Rep* 1970; 85: 587-99.
- 28 Barsoum IS, Mostafa MSE, Shihab AA, El-Alamy M, Habib MA, Colley DG. Prevalence of trachoma in school children and ophthalmological outpatients in rural Egypt. *Am J Trop Med Hyg* 1987; 36: 97-101.
- 29 Said ME, Goldstein H, Korra A, El-kashlani K. Distribution of visual acuity in Egypt. *Health Serv Rep* 1974; 89: 247-55.
- 30 Dawson CR, Jones BR, Tarrizo ML. *Guide to trachoma control*. Geneva: World Health Organisation, 1981.
- 31 EGRET. Statistics and Epidemiology Research Corporation, 909 NE 43rd Street, Seattle, WA 98105, USA.
- 32 Courtright P. Household clustering of trachoma and its role in the analysis of risk factors. Dr PH dissertation. Berkeley: University of California, 1988.
- 33 World Bank. *World Development Report 1989*. Washington, DC: World Bank, 1989.
- 34 Reinhardt J, Weber A, Nizetic B, Kupka K, Maxwell-Lyons F. Studies in the epidemiology and control of seasonal conjunctivitis and trachoma in southern Morocco. *Bull WHO* 1965; 39: 497-545.
- 35 Jones BR. The prevention of blindness from trachoma. *Trans Ophthalmol Soc UK* 1975; 95: 16-32.

Causes of blindness and visual handicap in the Central African Republic

Andrew R Potter

Abstract

The causes of bilateral blindness (best visual acuity less than 3/60) in 1371 people in the Central African Republic seen between 1985 and 1989 who attended eye clinics in 10 out of the 16 prefectures across the country are given. The main causes of bilateral blindness were cataract (51%), glaucoma (12.7%), and onchocerciasis (8.1%). In 710 patients with unilateral blindness the main causes were cataract (38%), glaucoma (10%), iritis (7.5%), and trauma (6.3%). Bilateral blindness in children was rarely seen. The causes of visual impairment (vision between 6/18 and 3/60) in 424 patients were cataract, including aphakia (38%), maculopathy (14%), and onchocerciasis (7%).

The Central African Republic is considered one of the poorest 20 countries in the world with a gross national product of 290 US\$ per head in 1986. It is a large landlocked country 622 436 km², two and a half times the size of the United Kingdom but with a population of less than 3 million in 1988. Life expectancy is estimated at 44 years, with a child mortality rate of 232. Health care is provided by the government medical service through hospitals in the larger towns and by an extensive network of voluntary church based hospitals and dispensaries.

The majority of people live by subsistence farming. The main crops are cassava, peanuts, bananas, plantains, maize, and rice. In certain areas cotton, coffee, and tobacco are produced as cash crops. In addition timber and diamonds are also exported.

The climate is tropical with little variation. Rains except in the far north of the country, are adequate, with an average of 60 inches (1500 mm) per year. The rainy season is from March until October.

Table 1 Causes of blindness in all age groups

Causes of blindness	Male n=887	Female n=484	Total n=1371	%
Cataract, including uncorrected aphakia	430	267	697	50.8
Glaucoma	125	49	174	12.7
Onchocerciasis	90	21	111	8.1
Optic atrophy	44	29	73	5.3
Iritis	39	24	63	4.6
Corneal scar	34	21	55	4.0
Phthisis bulbi	20	20	40	2.9
Trichiasis	7	16	23	1.7
Maculopathy	16	4	20	1.46
Retinopathy	12	2	14	1.0
Band keratopathy	6	2	8	0.55
Retinitis pigmentosa	2	5	7	0.51
Traditional medicines	2	5	7	0.51
Retinal detachment	5	1	6	0.44
Leprosy	4	1	5	0.36
Undiagnosed	15	2	17	1.24
All other causes	36	15	51	3.83

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Most of the population is well nourished, and child malnutrition is uncommon. The local diet is rich in palm oil, fresh fruits, and green leafy vegetables, so that vitamin A deficiency is rarely seen.

Ophthalmic services are poorly developed. There is a department of ophthalmology at the university hospital in the capital Bangui, with one full-time expatriate ophthalmologist. In the extreme north-west of CAR, near the border with Cameroon and Chad, there is a general physician who also performs eye surgery. Once a year a surgical team from West Germany spends one month visiting three or four provincial towns holding eye clinics and performing eye surgery.

Patients and methods

Between 1985 and 1989 the author visited 10 provincial hospital dispensaries and centres in 10 of the 16 prefectures, covering all regions except the sparsely populated north of CAR. A total of 7479 ophthalmic consultations were recorded. Visual acuity was recorded on both eyes of 424 patients. Causes of bilateral and unilateral blindness (visual acuity less than 3/60) and of visual impairment (visual acuity between 6/18 and 60) were recorded.

Results

Table 1 lists the major causes of blindness in 1371 blind patients attending eye clinics across CAR between 1985 and 1989. Cataract and uncorrected aphakia accounted for half the blindness. The ratio of blind men to women was 2:1. Onchocerciasis was four times more common in men than women. Trichiasis was twice as common in women as men. Glaucoma was twice as common in men.

Table 2 lists the causes of bilateral blindness in 30 blind children seen at the clinics. Corneal scar or phthisis bulbi accounted for 20% and congenital cataract for 13.5%.

The causes of unilateral blindness are given in Table 3. Cataract (38%) and glaucoma (10%) were the major causes. Trauma, onchocerciasis and optic atrophy were seen more frequently.

Table 2 Causes of bilateral blindness in children (0-15 yr)

Causes of blindness	Number	%
Corneal scar	5	17
Cataract	4	13
Optic atrophy	4	13
Iritis	3	10
Microphthalmia	3	10
Glaucoma	2	7
Trachoma	1	3
Phthisis bulbi	1	3
Other single causes	7	22
Total	30	100

Table 3 Causes of unilateral blindness in all age groups

Causes of blindness	Male n=499	Female n=211	Total	
			n=710	%
Cataract	194	77	271	38
Glaucoma	50	21	71	10
Corneal scar	49	17	66	9.3
Iritis	30	23	53	7.5
Trauma	35	10	45	6.3
Onchocerciasis	33	8	41	5.8
Phthisis bulbi	14	13	27	3.8
Optic atrophy	24	2	26	3.6
Maculopathy	11	8	19	2.7
Trichiasis	7	8	15	2.0
Other causes	52	24	76	11.0
Total	499	211	710	100

Table 4 Causes of unilateral blindness in children (0-15 yr)

Causes of blindness	Number	%
Trauma	8	27
Corneal scar	5	17
Cataract	5	17
Phthisis bulbi	4	13
Other	8	26
Total	30	100

Table 5 Causes of visual handicap in all age groups

Causes of blindness	Male n=272	Female n=152	Total	
			n=424	%
Cataract, including aphakia	95	66	161	38
Maculopathy	41	19	60	14.1
Onchocerciasis	23	8	31	7.3
Undiagnosed	9	14	23	5.4
Corneal scar	13	4	17	4.0
Iritis	10	5	15	3.5
Glaucoma	14	1	15	3.5
Refractive errors	11	4	15	3.5
Retinopathy	9	4	13	3.01
Entropion	4	8	12	2.8
Optic atrophy	7	3	10	2.35
Pterygium	5	1	6	1.4
Band keratopathy	3	2	5	1.1
All others	28	13	41	10.04
Total	272	152	424	100

men, whereas iritis, phthisis bulbi, maculopathy, and trichiasis were more common in women. Thirty children with unilateral blindness were seen. Corneal scar/phthisis bulbi (30%), trauma (27%), and cataract (17%) were the major causes (Table 4).

In all prefectures visited, except Ouham in the north-west of CAR, cataract was the commonest cause of bilateral blindness. In Ouham the commonest cause was onchocerciasis. Cataract was also the commonest cause of visual handicap (vision between 6/18 and 3/60) which, together with aphakia, contributed 38% of poor sight (Table 5).

Discussion

This survey is based on patients presenting to hospitals and clinics over a wide area of the Central African Republic between 1985 and 1989. There is therefore a bias to treatable conditions. For example, many have sought medical advice before and been told that there was no treatment possible. However, in several places visited no previous eye clinics have ever been held, and the incurably blind often retain the hope that a new doctor will, after all, be able to help them.

Not every prefecture in CAR was visited and these results cannot represent fully the spectrum

of blindness and visual handicap in the country. No study of the prevalence of blindness in CAR has yet been published.

Surveys from The Gambia, Tanzania, Chad, Ethiopia, Nigeria, Ghana, Kenya, and Malawi¹⁻⁷ all confirm cataract as the major cause of blindness in adults. However, variations in the major causes of blindness do occur owing to geographical and climatic differences. In dry areas trachoma is important, causing blindness from trichiasis and corneal scarring. In areas with fast flowing rivers onchocerciasis may occur. In countries with low rainfall, poor nutrition, and low measles immunisation coverage xerophthalmia may be frequently seen in children.

Cataract is the single most important cause of blindness in CAR and it accounts for half of the blind patients in this survey. If we assume a prevalence of blindness of 1% (similar to studies in other African countries - for example, The Gambia 0.7%, Kenya 0.9%, Chad 2.31%, Malawi 1.3%) then there are an estimated 28 600 blind people in CAR, half of whom are blind from cataract (approximately 14 000). Most of these people could have their sight restored through cataract surgery with aphakic spectacle correction. During the period 1985-9 there were three resident surgeons performing cataract surgery in CAR, and it is estimated that fewer than 500 patients were benefiting from sight restoring surgery per year. There is at present no optical workshop in CAR and all aphakic spectacles have to be imported (there are plans to start a workshop in Bangui).

It is unlikely that in the foreseeable future sufficient ophthalmologists will be available in CAR to deal with the cataract problem. Many of the blind live in rural communities and cannot travel to the capital city. One possible solution is to develop mobile teams of eye workers who will visit provincial hospitals to consult and provide surgery for the curably blind. General physicians and surgical nurses may be trained to perform intracapsular cataract extractions under local anaesthetic. Inexpensive aphakic spectacles (standard +10.00 or +11.00) will need to be made available to patients after cataract surgery.

Glaucoma accounts for 13% of blindness. Prevention of blindness from glaucoma poses a real problem in the developing world. Diagnosis depends on measuring intraocular pressure, examining the optic discs, and detecting visual field defects. Foster *et al* have shown that it is possible to train nurses to use the ophthalmoscope and examine the optic discs for pathological cupping.⁸ Surgical management by trabeculectomy appears the most practical therapy for rural patients in Africa, where supplies of pressure lowering drugs are erratic and expensive and where patient compliance is low.

Most interestingly, although onchocerciasis is the third cause of bilateral blindness, it is the predominant cause in the prefecture of Ouham, north-west CAR. It was only in this area that microfilariae were seen in the aqueous humour of patients. Further studies in this region should be undertaken with a view to mapping out the endemic focus, so that long term distribution of ivermectin can be undertaken. It is hard to know how much of the optic atrophy found in CAR is

related to onchocerciasis (and attempts to treat it with diethyl carbamazine). It would be interesting to see if with the introduction of ivermectin the number of new cases of optic nerve atrophy falls.

Few patients were seen with leprosy in CAR (six out of 3786 consultations in 1985-7). Blindness from leprosy is therefore rare, but it is often preventable if patients present in the early stages of the disease. Blindness from the topical application of traditional medication was also rarely seen, but with widespread education it could be abolished.

As few children with bilateral blindness were seen in the clinics it is hard to make much comment. Interestingly, however, blinding xerophthalmia was seen in only one patient during the first two years of the study (in a patient who had travelled from Zaire). This may be explained by the diet rich in vitamin A that is eaten in the rural areas. However, no visits were made to the two northernmost prefectures, where the climate is much drier and the diet may be less rich in palm oil and green leafy vegetables.

Patients who present with old corneal scars often give unhelpful histories that make it hard to determine the cause of their blindness. Many are reluctant to admit using traditional medicines for fear of an unsympathetic hearing.⁹⁻¹² Cataract and aphakia account for 38% of visual handicap, indicating again the pre-eminent position of cataract as a cause of visual impairment in Africa.

CONCLUSIONS

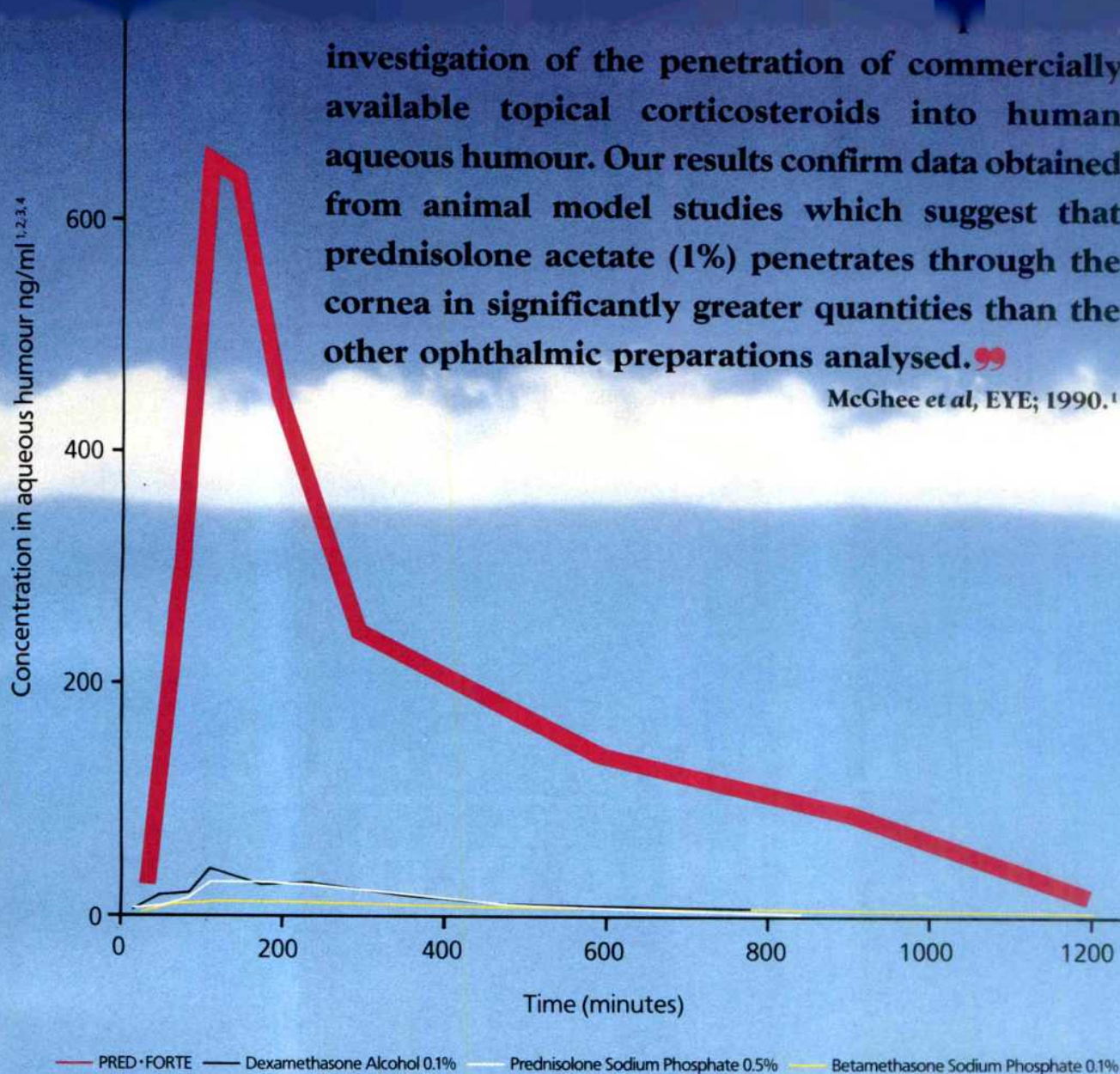
More than 14 000 people are blind from treatable cataract in the Central African Republic. The lack of trained personnel to deal with this problem is a major obstacle to eye care. Doctors, nurses, and other medical workers need training in eye care, and selected interested medical

personnel could be taught cataract surgery. The possibility of setting up mobile surgical teams should be considered. Ivermectin distribution programmes need to be urgently employed across CAR and especially in the north-west, to prevent further blindness in young and middle age adults from onchocerciasis. Health education, with reference to the treatability of cataract, the dangers of neglecting gradual loss of vision, and the dangers of applying traditional medicines to the eyes need to be implemented. Broadcasting information on national radio may be one way of achieving this.

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- 1 Faal H, Minassian D, Sowa S, Foster A. National survey of blindness and low vision in The Gambia. *Br J Ophthalmol* 1989; 73: 82-7.
- 2 Foster A, Taylor J. Causes of blindness in rural Tanzania. *East Afr J Ophthalmol* 1986; 7: 3-9.
- 3 Blindness in Chad. *WHO Weekly Epidemiological Record* 1987; 62: 322-3.
- 4 Quana'a P, Alemu B, Alemayehu W. Causes of blindness in the eye department of an Addis Ababa Hospital. *Ethiop Med J* 1986; 24: 19-23.
- 5 Ayanru JO. Blindness in the Mid Western State of Nigeria. *Trop Geogr Med* 1974; 26: 325-32.
- 6 Chatterjee S. Blindness in Ghana. *Ghana Med J* 1970; 9: 314-5.
- 7 Whitfield R, Schwab L, Ross-Degran D, Steinkuller P, Swartwood J. Blindness and eye disease in Kenya: ocular status survey results from the Kenya Rural Blindness Prevention Project. *Br J Ophthalmol* 1990; 74: 333-40.
- 8 Foster A, Wormald R, van der Heide A, Templeton K. Evaluation of ophthalmoscopy by non-ophthalmologists in diagnosing chronic glaucoma in West Africa. *Eye* 1989; 3: 647-50.
- 9 Chirambo MC, Tielsch JM, West KP, *et al*. Blindness and visual impairment in southern Malawi. *Bull WHO* 1986; 64: 567-72.
- 10 Sauter JJM. Xerophthalmic and measles in Kenya. Thesis. 1976. Kliniek voor Oogheelkunde, Rijks Universiteit Groningen, Netherlands.
- 11 McGlashan ND. Measles, malnutrition and blindness in Luapula province, Zambia. *Trop Geogr Med* 1969; 21: 157-62.
- 12 Foster A, Sommer A. Childhood blindness from corneal ulceration in Africa: causes, prevention and treatment. *Bull WHO* 1986; 65: 619-23.



investigation of the penetration of commercially available topical corticosteroids into human aqueous humour. Our results confirm data obtained from animal model studies which suggest that prednisolone acetate (1%) penetrates through the cornea in significantly greater quantities than the other ophthalmic preparations analysed. ⁹⁹

McGhee *et al*, EYE; 1990.¹

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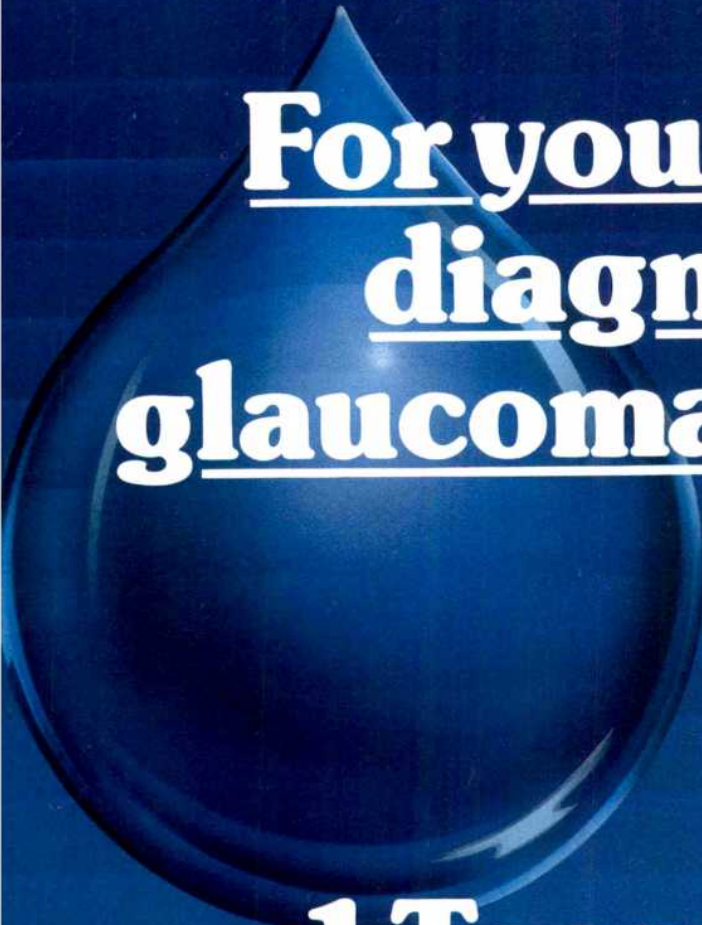
For routine inflammatory conditions of the eye

Pred-Forte™ Abbreviated Prescribing Information

Presentation Sterile ophthalmic suspension containing prednisolone acetate USP 1.0% (w/v) preserved with benzalkonium chloride Ph Eur 0.006% (w/v) and disodium edetate Ph Eur 0.0127% (w/v).
Uses For short-term treatment of steroid-responsive inflammatory conditions of the eye, after excluding the presence of viral, fungal and bacterial pathogens. **Dosage and administration** One to two drops instilled into the conjunctival sac two to four times daily. During the initial 24 to 48 hours the dosage may be safely increased to two drops every hour. **Contra-indications, warnings, etc** **Contra-indications:** Acute untreated purulent ocular infections. Viral diseases of the cornea and conjunctiva. Fungal diseases of the eye. Ocular tuberculosis. Hypersensitivity. **Warnings:** Acute purulent infections of the eye may be masked or enhanced by the use of topical steroids. Fungal invasion may be suspected in any persistent corneal ulceration where a steroid has been used, or is in use. Pred-Forte contains benzalkonium chloride and should not be used in patients continuing to wear soft (hydrophilic) contact lenses. **Use in pregnancy:** Animal studies indicate there may be a very small risk of abnormalities of foetal development if corticosteroids are administered during pregnancy. **Precautions:** Patients with a history of herpes simplex keratitis should be treated with caution. Use of Pred-Forte in the presence of stromal herpes simplex should be followed by frequent, mandatory, slit lamp microscopy. Use of topical corticosteroids may cause an increase in intraocular pressure in certain individuals. **Side-effects:** Ocular: Increased intraocular pressure; secondary ocular infections from fungi or viruses liberated from ocular tissues; perforation of the globe when used in conditions where there is a thinning of the cornea or sclera. Posterior subcapsular cataract formation has been reported. Systemic: Extensive topical use of corticosteroids may lead to systemic side effects. **Product Licence number** 0426/0051. **Basic NHS cost** 5 ml - £1.55; 10 ml - £3.09. **Product Licence holder:** Allergan Limited, High Wycombe, Bucks. HP12 3SH. Further information is available upon request to the above address. **References** 1. Penetration of Synthetic Corticosteroids into Human Aqueous Humour. McGhee C.N.J., Watson D.G., Midgley J., Noble M.J., Dutton G.N., Fern A.L., Eye 1990; 4: 526-530. 2. Penetration of Topically Applied Dexamethasone Alcohol into Human Aqueous Humour. Watson D.J., Noble M.J., Dutton N., Midgley J., Healey T., Arch Ophthalmol 106, May 1988, 686-687. 3. Comparative Studies of the Penetration of Synthetic Corticosteroids into the Human Eye by GC-NICIMS. Midgley J.M., McGhee C.N.J., Watson D.G., Noble M.J., Healey T., Dutton G.N., J Pharm Pharmacol 1988 Dec; 4(Suppl): 16P. 4. Penetration of Topically Applied Prednisolone Sodium Phosphate into Human Aqueous Humour. McGhee C.N.J., Noble M.J., Watson D.G., Dutton G.N., Fern A.L., Healey T.N., Midgley J.N., Eye 1989, 3, 463-467.

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References

1. Maclure, G.M. et al. 3rd Congress of European Glaucoma Society, 1988.
2. Kitazawa, Y. et al. Acta XXIV International Congress of Ophthalmology, 1983. P. Henkind (Ed), Lippincott, Philadelphia.
3. Hugues, F.C. et al. J. Fr. Ophthalmol. 1987; **10**, 8/9, 485-490.
4. Negishi, C. Acta Soc. Ophthalmol. Jpn. 1982; **85**, 57-66.
5. Scoville, B. et al. American Journal of Ophthalmology, 1988; **105**, No.2, 150-154.

Teoptic: Abbreviated prescribing information

Presentation: Sterile eye-drops containing carteolol hydrochloride 1% or 2% w/v with benzalkonium chloride 0.005% as a preservative.
Uses: Topical treatment for the reduction of intraocular pressure e.g. in ocular hypertension, chronic open angle glaucoma, some secondary glaucomas. **Dosage and administration:** Initially the recommended adult dose is one drop of Teoptic 1% Eye-drops in affected eye twice daily. If required the dosage may be altered to one drop of Teoptic 2% eye-drops in affected eye twice daily. *Children:* Use not recommended. *Elderly patients:* Recommended adult dose suitable. **Contra-indications:** Uncontrolled cardiac insufficiency. Bronchospasm, bronchial asthma, chronic obstructive pulmonary disease. Pregnancy. Hypersensitivity: **Precautions:** As with other topically applied ophthalmic preparations, Teoptic may be absorbed systemically. Therefore Teoptic should be used with caution in patients receiving systemic beta-blockers or with known contra-indications to systemic beta-blockers e.g. sinus bradycardia, second and third degree block, cardiogenic shock, uncontrolled diabetes.

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1. Duzman, E. *et al.*, Am J Ophthalmol 1982; 94 (3): 318-327. 2. Rakofsky S.J. *et al.*, Ophthalmology 1989; 96 (1): 8-11. 3. Wandel, T. *et al.*, Am J Ophthalmol 1986; 101: 298-304.



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Identifying anterior segment crystals

I W J Hurley, A M V Brooks, D P Reinehr, G B Grant, W E Gillies

Abstract

A series of 22 patients with crystals in the anterior segment of the eye was examined by specular microscopy. Of 10 patients with hypermature cataract and hyperrefractive bodies in the anterior chamber cholesterol crystals were identified in four patients and in six of the 10 in whom aspirate was obtained cholesterol crystals were demonstrated in three, two of these having shown crystals on specular microscopy. In 10 patients with intra-corneal crystalline deposits, cholesterol crystals were found on specular microscopy, including one case of Schnyder's crystalline corneal dystrophy. Of two patients with multiple myeloma, corneal crystals were demonstrated in one. Crystals of the anterior segment of the eye are most likely to be cholesterol, and identification is important for future treatment.

Diagnosis of the nature of crystalline deposits seen in the anterior segment of the eye may form the basis of treatment. Though uncommon, crystalline deposits may occur in a wide variety of conditions^{1,2} and it is important to differentiate those associated with a variety of general medical conditions from those occurring in local corneal disease, such as old corneal scarring, or those associated with the recently described infectious crystalline keratopathy.³⁻⁶

We have studied a series of patients who presented with crystalline deposits in the cornea and in the anterior chamber of the eye, identifying these crystals by specular microscopy and also by light microscopy when an aspirate from the anterior chamber could be obtained. The value of these findings in the diagnosis of the underlying condition is discussed.

Materials and methods

A series of 22 patients were studied with various types of crystal in the anterior segment. Ten patients, six males and four females, mean age 71 (SEM 5) years, range 44 to 84 years, had crystals in the anterior chamber associated with a hypermature cataract. Another 12 patients, three males and nine females, aged 64 (SEM 4) years, range 42 to 83 years, were examined for crystalline deposits in the cornea, including two patients with multiple myeloma.

Specular microscopy was performed with the wide-field Pocklington contact specular microscope (Konan Camera Research Inc, Hyogo, Japan) after the instillation of topical oxybuprocaine hydrochloride 0.4% (Benoxinate), without a contact lens. Conventional and relief mode specular microscopy pictures were obtained by our previously described technique.^{7,8} The relief mode^{7,9,10} enables the observer to view the

changes taking place on the posterior surface of the corneal endothelium. Photographs were taken of the central cornea and also above, below, and to either side in an extensive pattern. A Minolta XD-5 camera with data back was attached to the specular microscope. Kodak Tri-X 135 film was used and developed in D 76 developer for 13 minutes at 23°C. Corneal deposits were examined by coming forward to focus on these deposits at various levels in the corneal stroma. Crystals in the anterior chamber could be demonstrated by focusing back into the anterior chamber, which allowed visualisation of deposits on the posterior surface of the cornea as well as material circulating in the anterior chamber of the eye.

Fresh anterior chamber aspirate was obtained in six patients with hypermature cataract and phacolytic glaucoma and was examined by direct microscopy, without the use of xylol or alcohol in order to avoid dissolving the crystals.

Patients were derived from the authors' practices or hospital outpatients seen from 1985 to 1990. Ethical approval was provided by the Research and Ethics Advisory Committee of the hospital and informed consent was obtained from all subjects.

Results

Of the 22 patients there were 10 with hypermature cataract and refractile bodies in the anterior chamber, 10 with hyperrefractive granules in the cornea, and two with multiple myeloma, one having superficial fine particulate corneal opacities. Ten patients with a hypermature cataract showed hyperrefractive granules in the anterior chamber on slit-lamp biomicroscopy (Fig 1). On specular microscopy crystals were demonstrated on the posterior corneal surface or in the anterior chamber in four of these 10 patients. These crystals had a typical rectangular appearance consistent with cholesterol crystals (Fig 2), though the notched corner typical of cholesterol could not always be



Figure 1 Slit-lamp biomicroscopy of the left eye of a 55-year-old male with a hypermature cataract shows dense exudate with hyperrefractive bodies in the anterior chamber.

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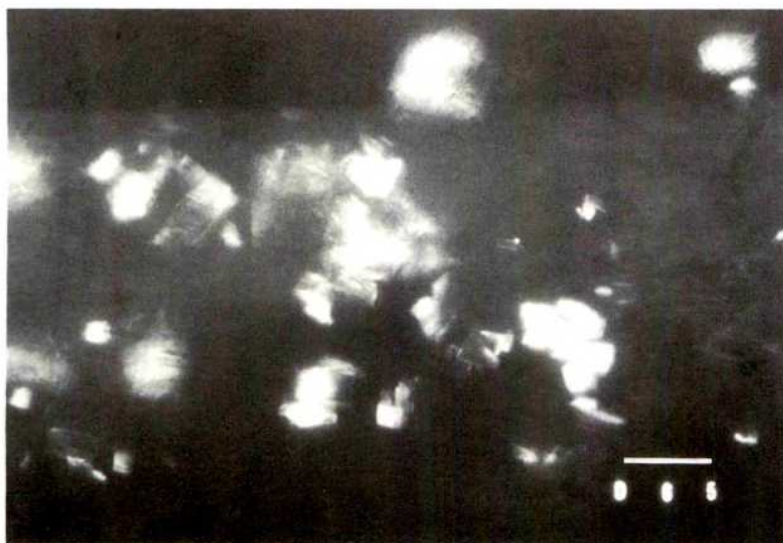


Figure 2 Specular microscopy of the same eye as Figure 1 shows numerous rectangular light crystalline structures consistent with cholesterol crystals. (Bar=100 μ m.)

identified. The presence of these crystals was subsequently confirmed in anterior chamber aspirate in two of these patients who were among the six patients on whom anterior chamber aspiration was performed. Of the six patients in whom crystals were not demonstrated on specular microscopy it was not possible to obtain any detail on specular microscopy owing to corneal oedema in three patients, while in the other three it was possible to obtain detail but not to see crystals. Fresh anterior chamber aspirate was obtained in six of the 10 patients with hypermature cataract, and in three of these typical crystals were demonstrated, including two patients in whom crystals were seen on specular microscopy. These crystals were birefringent to polarised light (Fig 3).

There were 10 patients with various local corneal conditions in whom possible corneal crystals were seen clinically on slit-lamp biomicroscopy. These included five patients with old quiescent vascularised corneal scars, two with old seronegative interstitial keratitis, one with Schnyder's crystalline corneal dystrophy, one with an old corneal graft, and one with marginal degeneration of the cornea. Specular microscopy in all these patients showed light rectangular crystalline structures (Figure 4) con-

Figure 4 Specular microscopy of the right eye of a 70-year-old female with deposits of crystals in an old area of vascularised scarring shows rectangular crystals in the corneal stroma consistent with cholesterol crystals. Arrow indicates a notched corner. (Bar=100 μ m.)

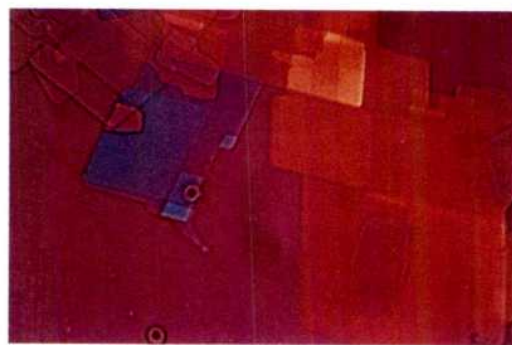
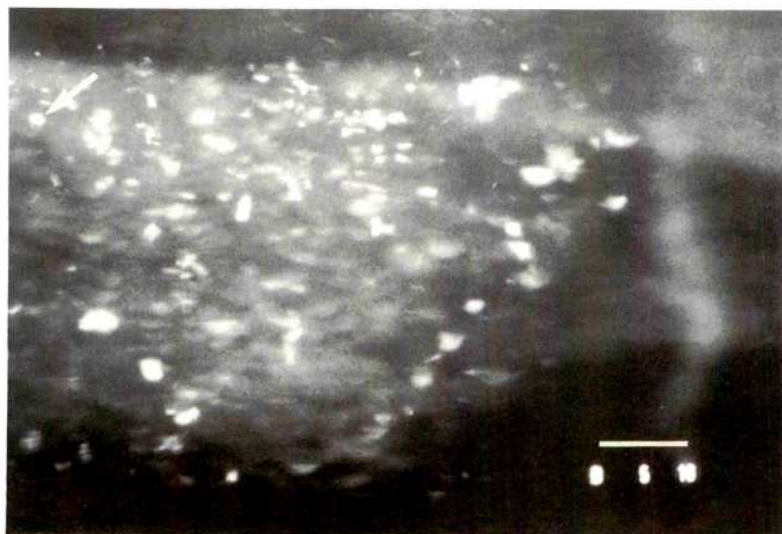


Figure 3 Anterior chamber aspirate from the same eye as in Figures 1 and 2. Under polarised light birefringent flat rectangular notched crystals of cholesterol are seen. (Original magnification, $\times 2500$.)

sistent with cholesterol, though a notched corner could not always be demonstrated.

In one of the two patients with multiple myeloma numerous fine superficial corneal opacities were seen on slit-lamp biomicroscopy. Specular microscopy showed numerous light stick-like structures of uniform thickness with rounded ends arranged irregularly at angles to each other. They ranged from 1 to 4 endothelial cell diameters in length (Fig 5) and were consistent with myeloma crystals.

Discussion

Establishing the exact nature of crystalline structures in the anterior segment of the eye presents a clinical problem, as biopsy is usually not possible. Although it is possible to examine an anterior chamber aspirate, this is an invasive procedure, and identification of the crystals may be required before operation is undertaken. It may be very difficult to obtain material which can be usefully examined by corneal biopsy, especially if the deposits are deep, while specular microscopy is a simple non-invasive means of identification.

In the present cases most of the crystals were cholesterol, and these could be identified because of their regular geometric form, though a notched corner was not always apparent as the crystals could overlap each other or be seen edge on. However, some discrete crystals were usually seen, and their morphology differed from that described for the deposits of infectious crystalline keratopathy, whose exact nature is still not clearly established¹¹ and whose differentiation has important treatment implications. The cholesterol crystalline deposits seen in our cases were static or only very slowly progressive and most were associated with old quiescent vascularised keratopathy of various causes, including one patient who had a corneal graft, two others with old interstitial keratitis, and one with marginal corneal degeneration with little vascularisation.

The morphology of deposits seen in our case with multiple myeloma was distinctive and different from the cholesterol deposits seen in the other cases. One report of deposits in multiple myeloma described crystalline deposits within the endoplasmic reticulum of plasma cells,¹² another crystals in the cytoplasm of keratocytes,¹³ while another report¹⁴ described needle-like elec-

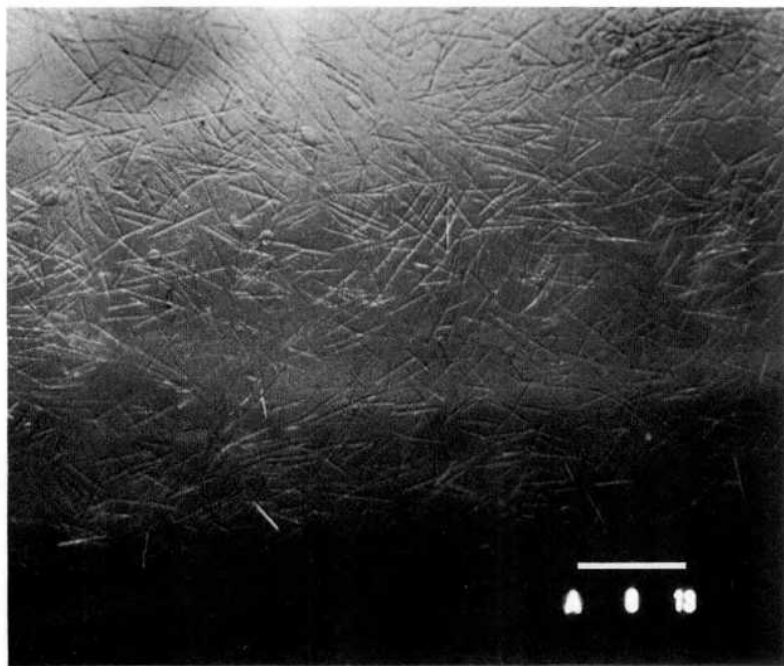


Figure 5 Specular microscopy of the left eye of a 61-year-old female with multiple myeloma showing numerous small stick-like crystalline structures lying at different angles to each other, consistent with myeloma crystals. (Bar=100 μm .)

tron-dense extracellular particles in the cornea at all levels. In our patient the numerous light stick-like structures seen on specular microscopy were up to 4 endothelial cell diameters in length, which strongly supports an extracellular location for these crystals.

Although other crystalline deposits have been described in the cornea, our experience suggests that corneal crystalline deposits are most likely to be cholesterol, as are the hyperrefractive granules in the anterior chamber of patients with hypermature cataract. Specular microscopy may

be used to identify these crystals, thus providing a basis for clinical diagnosis and subsequent management without the need for invasive biopsy.

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- 1 Brooks AMV, Grant G, Gillies WE. Determination of the nature of corneal crystals by specular microscopy. *Ophthalmology* 1988; **95**: 448-52.
- 2 Brooks AMV, Grant G, Gillies WE. Comparison of specular microscopy and examination of aspirate in phacolytic glaucoma. *Ophthalmology* 1990; **97**: 85-9.
- 3 Gorovoy MS, Stern GA, Hood CI, Allen C. Intrastromal noninflammatory bacterial colonization of a corneal graft. *Arch Ophthalmol* 1983; **101**: 1749-52.
- 4 Meisler DM, Langston RHS, Naab TJ, Aaby AA, McMahon JT, Tubbs RR. Infectious crystalline keratopathy. *Am J Ophthalmol* 1984; **97**: 337-43.
- 5 Sutton GL, Miller RC, Robinson LP. Infectious crystalline keratopathy. *Aust NZ J Ophthalmol* 1990; **18**: 151-3.
- 6 Pararajasegaram P, Mower G, Barras CW, Coster DJ. An unusual case of crystalline keratopathy. *Aust NZ J Ophthalmol* 1990; **18**: 155-7.
- 7 Brooks AMV, Grant G, Gillies WE. Differentiation and assessment of corneal endothelial changes associated with diseases of the anterior segment of the eye. *Aust NZ J Ophthalmol* 1987; **15**: 65-70.
- 8 Brooks AMV, Grant G, Gillies WE. The influence of superficial epithelial keratopathy on the corneal endothelium. *Ophthalmology* 1989; **96**: 704-8.
- 9 Hartmann C. Die 'indirekte' Spiegelmikroskopie. *Ophthalmologica* 1981; **183**: 177-86.
- 10 Sherrard ES, Buckley RJ. The relief mode. *Arch Ophthalmol* 1982; **100**: 296-300.
- 11 Samples JR, Baumgartner SD, Binder PS. Infectious crystalline keratopathy: an electron microscope analysis. *Cornea* 1985-6; **4**: 118-26.
- 12 Hoisen H, Ringvold A, Kildahl-Andersen O. Corneal crystalline deposits in multiple myeloma. A case report. *Acta Ophthalmol (Kbh)* 1983; **61**: 493-500.
- 13 Barr CC, Gelender H, Font RL. Corneal crystalline deposits associated with dysproteinemia. Report of two cases and review of the literature. *Arch Ophthalmol* 1980; **98**: 884-9.
- 14 Miller KH, Green WR, Stark WJ, Wells HA, Mendelsohn G, Kanhofer H. Immunoprotein deposition in the cornea. *Ophthalmology* 1980; **87**: 944-50.

Dominant cone dystrophy starting with blue cone involvement

Mary J van Schooneveld, Loe N Went, Jendo A Oosterhuis

Abstract

The results of ophthalmological and colour vision studies are reported on 13 patients from a family with a dominant cone dystrophy spanning seven generations. The onset of visual deterioration occurred in the third or fourth decade. In the early stages of the disease, when visual acuity is still close to normal, a severe defect in the blue sensitivity is already present, as measured by spectral sensitivity curves and other tests suitable for the detection of tritan defects. In our opinion this condition represents a distinct entity with autosomal dominant inheritance.

Cone dystrophies form a heterogeneous group of disorders characterised by progressive impairment of visual acuity and colour vision, photophobia, and a low or absent photopic electroretinogram.¹⁻⁶ Symptoms may start in early childhood or as late as the fifth decade, the great majority of cases presenting within the first two decades of life.^{4,6} A considerable proportion of cone dystrophies are inherited, usually in an autosomal dominant fashion, but occasionally as a sex-linked^{7,8} or autosomal recessive^{4,9} disorder.

Fundus changes, if present, consist of patchy macular mottling, a bull's eye lesion, or more widespread atrophic changes. At the onset of symptoms most patients do not show any fundus abnormalities.⁶

Colour vision disturbances are reported to be usually of the red-green type in the early stages.⁶ Later on non-specific disturbances are found, and eventually all colour discrimination is lost. Pearman *et al*³ found in their study of nine affected members of a family with autosomal dominant cone dystrophy that any type of colour vision defect could occur in the early stages, though a red-green defect was usually found. In one patient a strong tritan defect was found in addition to red-green disturbances.

In this paper we report on a family with autosomal dominant cone dystrophy with selective early blue cone involvement which differs from previously described cases. Loss of visual acuity occurs relatively late in life, around the age of 20 to 35 years, and is only slowly progressive. In many patients the fundus appears normal.

Methods

Ophthalmic examinations included assessment of visual acuity, slit-lamp examination, and ophthalmoscopy in all 13 patients; electroretinography (ERG) in 10, fluorescein angiography and visual field examination in six.

The following colour vision tests were employed: the Ishihara, the Hardy-Rand-Rittler (HRR) and 'Birch'¹⁰ plate tests; the Farnsworth Panel D15 and Lanthony desaturated Panel D15 arrangement tests; the Nagel anomaloscope; an

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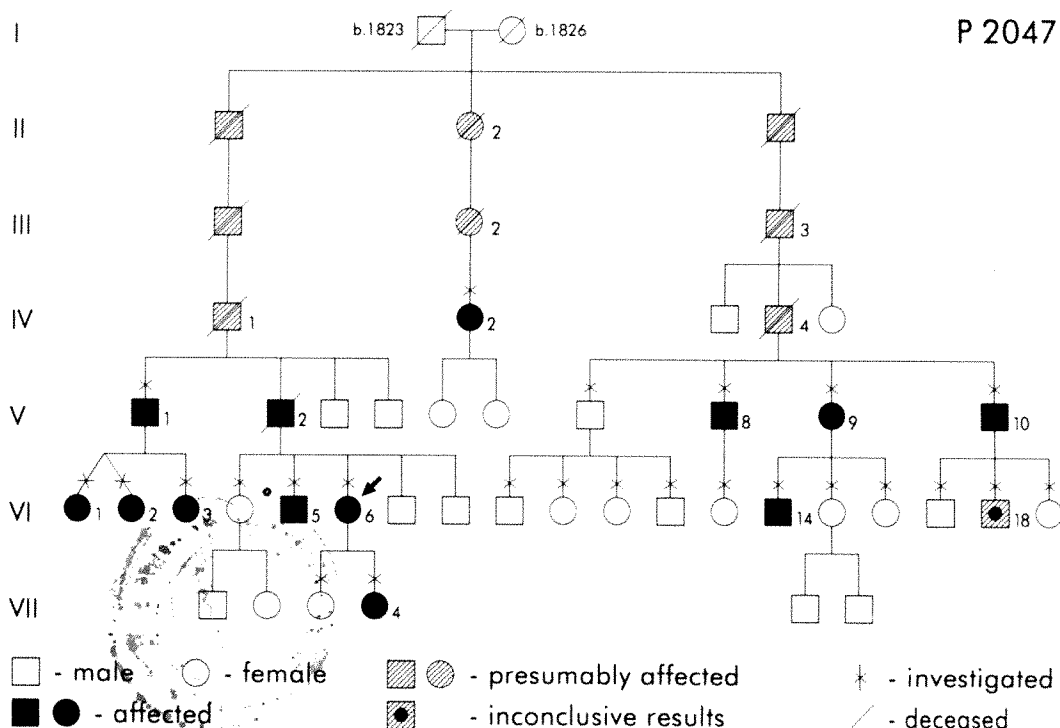


Figure 1 Pedigree of the family.

instrument for measuring spectral sensitivity curves^{11,12} and a so called 'tritan test'.¹³ The Birch plate test consists of nine plates, five of which are specifically designed to detect a tritan defect. The 'tritan test' has a 1° flickering (frequency 0.5 Hertz) blue (462 nm) test field on a 14° intense yellow background with a luminance of 3700 cd/m². The blue test field may be presented attenuated with a 2.6 neutral density filter or unattenuated. Tritan defective individuals fail to see the attenuated stimulus, even after a long exposure, while normal individuals see it within 30 to 60 seconds of adaptation.

Results

In Figure 1 an abbreviated version of the pedigree is given. Seven generations are involved dating back as far as 1823. The family history on members of the second, third, and fourth generation (photophobia and severe impairment of visual acuity, starting gradually in later adult life) is highly suggestive of the presence of the abnormal gene. With one exception (IV.2) only individuals from the fifth to the seventh generation were alive and available for examination. From the pedigree the autosomal dominant mode of inheritance is obvious: males and females are equally affected, father to son transmission is present, and roughly half the children of affected individuals are affected themselves. A few case histories revealing the typical abnormalities and the marked variability of the disorder will be presented.

CASE HISTORIES

VI.6, the index case, was born in 1950. At the age of 5 she was operated on for strabismus. At age 12 her corrected visual acuity was 0.2 OD and 1.0 OS, with a normal fundus aspect. The right eye was considered to be amblyopic. These findings were unchanged at age 21 and 26. When 31 she visited the Eye Clinic in Leiden because of reading problems. Corrected visual acuity of the left eye was 0.9 and fluorescein angiography showed minute window defects in the maculae.

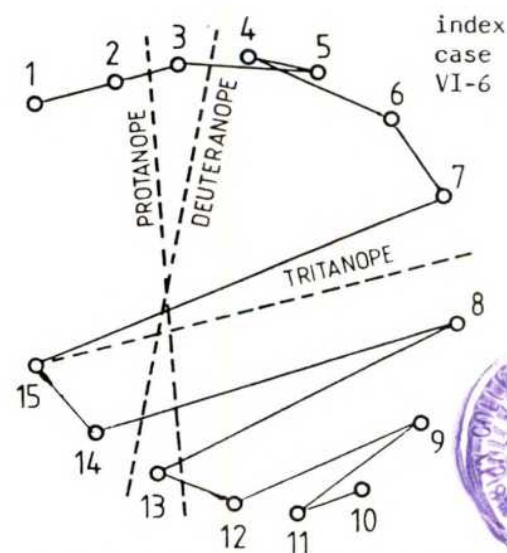


Figure 2 Results of the F15 arrangement test on the index case (VI.6).

Goldmann kinetic perimetry revealed a mild relative central scotoma for both eyes. The ERG showed a normal rod response and a decreased cone response (50% of the normal amplitude). The F15 arrangement test revealed a classical tritan response (Fig 2), in accordance with the almost complete absence of blue sensitivity on the spectral luminosity curves (between 2 and 3 logarithms below the normal reading) and a tritan response with the 'tritan test'. She accepted a practically normal red-green setting with the Nagel anomaloscope, though she could not distinguish any of the plates of the Ishihara and HRR tests presumably because of the central scotoma. In this patient central vision started to decrease relatively late in life; at the age of 35 her visual acuity was still 0.8.

VI.5, a brother 1½ years older than the index case, had corrected visual acuity of 0.8 in both eyes at the age of 18, with a normal fundus appearance. At age 32 his visual acuity had decreased to finger counting at 2 m for both eyes, with a large central scotoma. The patient was photophobic. Ophthalmological examination at age 34 revealed pallor of the optic discs and marked pigmentary mottling in the macular area. Angiography disclosed bilateral symmetrical window defects (Fig 3). The electro-oculogram (EOG) was normal; the ERG showed a normal rod response, while the cone mediated response was reduced to 25% of the normal amplitude. The patient could not perform any of the colour vision tests.

V.9, a 50-year-old woman, noted decreasing visual acuity in her early 30s. At age 32 corrected visual acuity was 0.2 OD and 0.3 OS. Fluorescein angiography showed no abnormalities except for myopic changes. Colour vision was reported to be greatly disturbed. At the age of 50 visual acuity in both eyes had decreased to counting fingers. We noted a marked discrepancy between functional deficit and fundus findings, since ophthalmoscopy revealed only subtle granular pigmentation of the macula. On angiography minute window defects of the retinal pigment epithelium were seen. There was marked photophobia. The ERG showed mainly scotopic responses; with red stimuli no responses

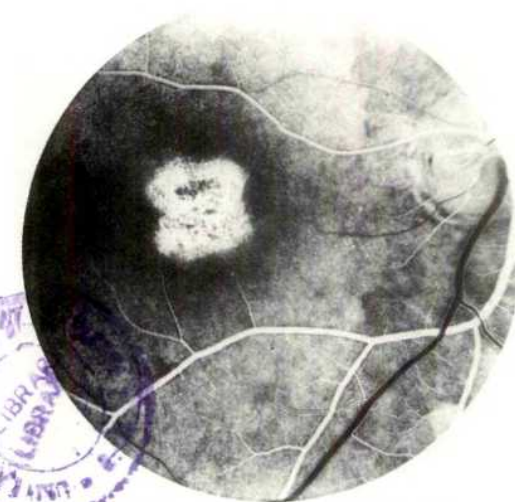


Figure 3 Fluorescein angiography of VI.5 showing extensive window defect.

Table 1 Data of 13 individuals with dominant cone dystrophy

Pedigree number	Sex	Age ¹	Visual acuity ²		Refractive error ³		Fundus ⁴	ERG ⁵	Birch ⁶	TT ⁷	Curves ⁸
			OD	OS	OD	OS					
IV.2	F	76	LP/LP		-16/-16		++	+	*	*	*
V.1	M	62	CF/CF		0/0		++	+	*	*	*
V.2	M	44	CF/CF		-7/-9		+				
V.8	M	53	CF/CF		-9/-10		-	+	*	*	*
V.9	F	50	CF/CF		-4/-5		+	+	*	*	*
V10	M	43	0.3/0.3		-4/-4		-		4	t	t
VI.1	F	33	0.2/0.3		+1/0		-	+	5	t	t
VI.2	F	33	0.8/0.6		-1/-1		-	+	3	t	t
VI.3	F	26	0.5/0.6		0/0		-	+	3	t	t
VI.5	M	34	CF/CF		-1/-1		++	+	*	*	*
VI.6	F	35	0.2/0.8		0/0		+	+	5	t	t
VI.14	M	26	0.8/0.8		-1/-1		-	-	2	t	t
VII.4	F	8	1.0/1.0		0/0		-		2	t	t

- 1 Refers to age at last examination.
- 2 Decimal acuity following Snellen notation; LP=light perception; CF=counting fingers.
- 3 Spheric equivalent in dioptres.
- 4 Normal aspect or only dubious changes like absent foveolar reflex; +=discrete atrophic changes at funduscopy or fluorescein angiography; ++=marked pigmentary dystrophy or areolar atrophy.
- 5 Electroretinography; +=absent or reduced photopic ERG; -=normal ERG.
- 6 Birch test: the number of tritan plates missed (maximally 5).
- 7 Tritan test.
- 8 Spectral sensitivity curves, with and without yellow bleaching; *test impossible due to low vision.
- 9 In this man there were also myopic macular changes like Fuchs's spot.

were obtained. Colour vision testing had become impossible.

VI.14, the 26-year-old son of V.9, had noted some difficulty in distinguishing blue from green. Corrected visual acuity was 1.0 in both eyes at the age of 20 and 0.8 at the age of 26. Ophthalmoscopy showed normal optic discs and normal maculae except for absent foveolar reflexes. Both the photopic ERG (also with red stimuli) and the scotopic ERG were normal. However, the results of the F15, HRR, and Birch tests were suggestive of impairment of the blue cone sensitivity. This was definitely proved by the results of the 'tritan test' and by the luminosity curves, which showed an almost complete loss of blue cone sensitivity (more than 2 logarithms below normal). Not a single mistake was made with the Ishihara and with the red-green plates of the HRR test.

In Table 1 a summary is given of the clinical and colour vision findings in all 13 affected individuals. Myopia of at least 4 dioptres was found in five of them. The macular appearance was normal or inconspicuous in about half of the patients, but distinctive in two: VI.5 had exten-

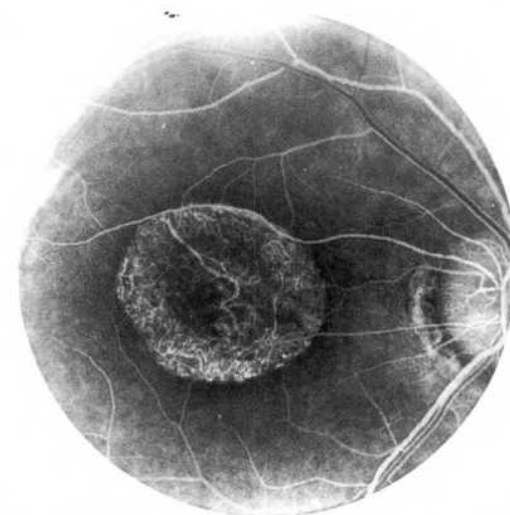


Figure 4 Fluorescein angiography of V.1 showing areolar atrophy of the macula.

sive loss of the central retinal pigment epithelium (Fig 3), and V.1 had areolar atrophy of the macula (Fig 4). IV.2 had definite areolar atrophy in both maculae, but also widespread atrophic changes due to her high myopia of 16 dioptres. She had a history of progressive loss of colour vision starting very early in life, and her photopic ERG was almost absent at the age of 53; this was considered to be not compatible with high myopia only. The information on V.2, who died in 1970 at the age of 50, was obtained from another ophthalmologist. His visual acuity had deteriorated from 0.5 OD and 0.1 OS at the age of 34 to counting fingers at the age of 44. His macular abnormalities (Fuchs's spot) could be ascribed to his myopia (7 and 9 dioptres respectively). Nevertheless, this man must have been a gene carrier, since two of his children are affected.

In 10 patients ERG studies were performed and in nine the photopic ERG was reduced or absent. Only in patient VI.14, with subnormal visual acuity was a normal ERG found, while with colour vision testing a tritan disturbance was present. This patient was therefore considered to be affected. It is to be expected that the ERG in this patient will become abnormal in time. The two brothers of V.1 and V.2 as well as the two youngest sons of V.2 could not be examined because they were living abroad. They were said to be without any visual complaints.

In Fig 5 the visual acuity in the better eye is plotted against age for the 13 affected individuals. Although there is considerable variation at any given age, visual loss has a tendency to start in the third or fourth decade, usually leading to loss of central vision in the fourth or fifth decade. Visual acuity of 0.8 or more was present in four affected family members, the oldest being 35 years, but one member (VI.5) had already a nearly complete loss of central vision at the age of 34 years. The decrease of visual acuity was remarkably slow, for instance from 1.0 to 0.8 in nine years (VI.6) and from 0.7 to 0.3 in 22 years (V.10). Central vision was lost in all affected family members older than 50 years.

In the early stages of the disease a tritan defect was a consistent finding. The results of the three

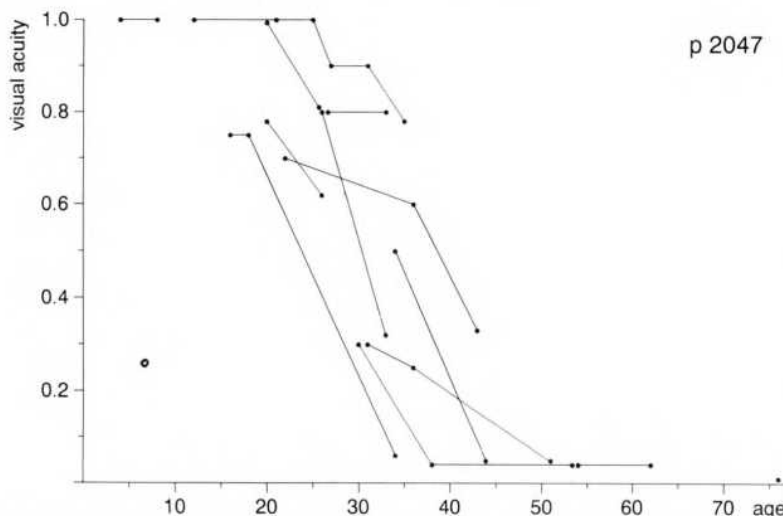


Figure 5 Visual acuity related to age in 13 patients. Points connected by a line are different measurements on the same patient.

Figure 6 Spectral sensitivity curves of VI.2 compared with results of a normal individual. A: Normal white background (retinal illumination 3.9 log troland). B: Yellow background (OG filter, retinal illumination 5.3 log troland).

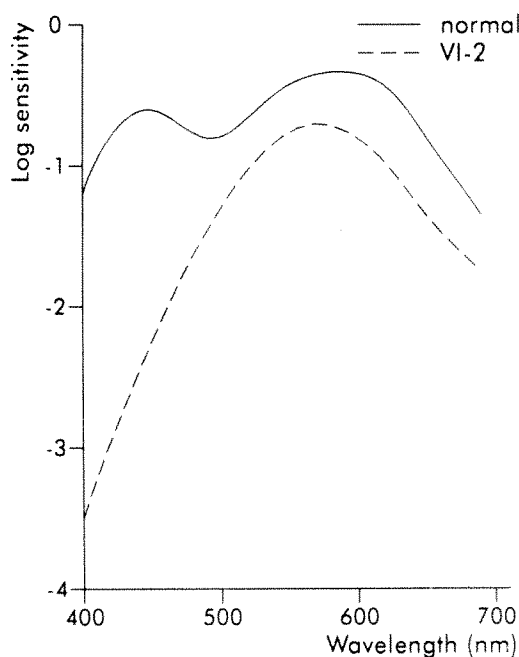


Figure 6A.

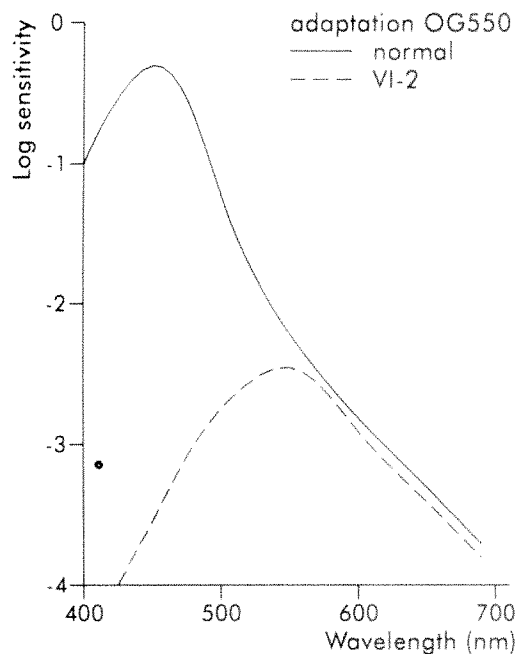


Figure 6B.

most specific tritan tests are listed in Table 1. The Ishihara plates were either correctly seen or non-specific errors were made. The HRR plates and the D-15 desaturated panel pointed to a tritan defect in four persons but gave almost normal results in two (VI.2 and VI.3); the visual acuity of the other patients was too low for us to perform these tests. Two patients (VI.2 and VI.6), who made numerous errors with the Ishihara plates presumably because of loss of central vision, chose a normal matching range with the Nagel anomaloscope. The spectral sensitivity curves were diagnostic for the absence of blue sensitivity (Fig 6 A, B).

Discussion

We describe a family with an autosomal dominantly inherited cone dystrophy associated with loss of blue cone function as an early sign. In this family the diagnosis of cone dystrophy is firmly established by the presence of the characteristic symptoms: loss of visual acuity, decreased or absent photopic ERG, photophobia, and colour vision deficiency.

Cone dystrophy can be associated with a normal aspect of the macula, but, if macular lesions develop, three types can be distinguished according to Krill¹: a bull's eye lesion, diffuse spotty pigment clumping, and choroidal vascular atrophy. In our family we found in seven patients a normal fundus appearance or only the absence of macular reflexes (Table 1). When maculopathy was visible, it presented mostly as diffuse pigment mottling. In two patients (IV.2 and V.1) extensive areolar macular atrophy was present, which in IV.2 could also be related to her high myopia. The progression of the pigmentary maculopathy was remarkably slow: in two patients (V.8 and V.9) it hardly progressed over the course of 19 years, notwithstanding considerable loss of visual acuity.

Myopia of at least 4 dioptres was found in five of the affected 13 individuals, which may be a

chance finding. However, cone dystrophy and myopia can be correlated, as was found in a large family with X-linked cone dystrophy studied by some of us⁷ in which 15 of the 17 affected males and five of the 31 obligate carriers had high myopia. Myopia might also be a separate hereditary trait in our family, since the unaffected elder brother of V.8 also had high myopia. Visual acuity, fundus appearance, and colour vision testing in this 55-year-old man were entirely normal. In our family early blue cone involvement was a consistent and prominent diagnostic finding. All persons with sufficient vision to perform colour vision tests were found to be tritan defective (Table 1). Some even reported impaired blue-green discrimination from early childhood (IV.2, VI.3, and VI.5). In patient VI.14, with a normal photopic ERG, defective blue cone function and a mild reduction of visual acuity were the only obvious signs of the dominant cone dystrophy.

Since the condition starts insidiously, patients may not seek medical advice until visual acuity has dropped below 0.5, because they adapt to their slowly developing visual handicap.

Marré *et al*¹⁴ discussed a family with dominant cone dystrophy from which six individuals were examined in detail. Two of them had too low visual acuity to perform most of the colour vision tests. Apart from red-green disturbances Marré *et al* found blue cone involvement, except for their youngest patient, 12 years old, who had visual acuity 0.6 and normal colour vision test results. This contrasts with our family, in which tritan deficiency precedes loss of visual acuity. Furthermore, the condition in their family followed a more progressive course leading to substantial visual loss before the age of 20.

Recently Bresnick *et al*¹⁵ described a family with 'autosomal dominant macular dystrophy with preferential short-wavelength sensitive cone involvement'. This title might suggest that the condition is comparable or identical to the one present in our family. However, in contrast

to our family, the patients of Bresnick *et al* retained good visual acuity at mature age (1.3 in a 40-year-old female and 1.0 in a 36-year-old male); moreover fluorescein angiography and conventional ERG were normal except for delayed implicit times. In their family the tritan defect is comparable to that in our family, but the ophthalmological findings are different. In conclusion, we believe that the family we have described with dominant cone dystrophy presenting initially as a tritan defect, represents a previously undescribed entity.

Unequal recombination or gene conversion of the genes on the long arm of the X-chromosome coding for the production of red and green cone visual pigments may cause congenital colour vision deficiency.¹⁶ DNA studies in a family with X-linked cone dystrophy with predominant loss of red cone function in the early stages, recently described by Reichel *et al*,⁸ revealed a 6.5 kilobase deletion within the red cone pigment gene. This observation made us wonder whether the tritan gene on chromosome 7 could be responsible in our family for dominant cone dystrophy. Dr C. J. Weitz in Baltimore was willing to examine leucocyte DNA from our patient VI.2. He comments: 'The blue sensitive visual pigment locus was indistinguishable from that of normal controls by Southern blot and by denaturing gradient gel electrophoresis of "GC-clamped" polymerase chain reaction products containing the exons and adjacent non-coding sequences. These results exclude any insertion or deletion larger than about 100 base pairs and make unlikely but do not exclude any smaller rearrangements or a point mutation within the gene' (Weitz C J, and Nathans J, personal communication 1990). Future DNA studies may enable us to make accurate subdivisions of the

different cone dystrophies and could help us to understand the disease process in greater detail.

The authors are grateful to Mrs I van Leeuwen-Cornelisse for her help in the initial stages of the family study and to Dr C J Weitz for the DNA studies on patient VI.2.

- 1 Berson EL, Gouras P, Gunkel RD. Progressive cone degeneration, dominantly inherited. *Arch Ophthalmol* 1968; 80: 77-83.
- 2 Krill AE, Deutman AF. Dominant macular degenerations: the cone dystrophies. *Am J Ophthalmol* 1972; 73: 352-69.
- 3 Pearlman JT, Owen WG, Brounly DW, Sheppard JJ. Cone dystrophy with dominant inheritance. *Am J Ophthalmol* 1974; 77: 294-303.
- 4 Krill AE. Cone degenerations. In: Krill AE, Archer DB, eds. *Krill's hereditary retinal and choroidal diseases: clinical characteristics*. New York: Harper and Row, 1977; 2: 421-78.
- 5 Ripps H, Noble KG, Greenstein VC, Siegel IM, Carr RE. Progressive cone dystrophy. *Ophthalmology* 1987; 94: 1401-9.
- 6 Weleber RG, Eisner A. Cone degeneration ('Bull's eye dystrophies') and color vision defects. In: Newsome DA, ed. *Retinal dystrophies and degenerations*. New York: Raven, 1988; 154; 162, 233-56.
- 7 Keunen JEB, Everdingen JAM van, Went LN, Oosterhuis JA, Norren D van. Color matching and retinal densitometry in patients and carriers of an X-linked progressive cone dystrophy. *Arch Ophthalmol* 1990; 108: 1713-9.
- 8 Reichel E, Bruce AM, Sandberg MA, Berson EL. An electroretinographic and molecular genetic study of X-linked cone degeneration. *Am J Ophthalmol* 1989; 108: 540-7.
- 9 Gouras P, Eggers HM, MacKay CJ. Cone dystrophy, nyctalopia and supernormal rod responses. *Arch Ophthalmol* 1983; 101: 718-24.
- 10 Birch-Cox J. Design of diagnostic test for congenital and acquired colour vision defects. In: Verriest G, ed. *Colour vision deficiencies*. Basel: Karger, 1976; 4: 196-201.
- 11 Vries-de Mol EC de, Went LN, Norren D van, Pols LCW. Increment spectral sensitivity of hemizygotes and heterozygotes for different classes of colour vision. *Mod Probl Ophthalmol* 1978; 19: 224-8.
- 12 Went LN, Pronk N. The genetics of tritan disturbances. *Hum Genet* 1985; 69: 255-62.
- 13 Norren D van, Went LN. New test for the detection of tritan defects evaluated in two surveys. *Vision Res* 1981; 21: 1303-6.
- 14 Marré M, Marré E, Zenker H-J, Fülle D. Colour vision in a family with dominant progressive cone dystrophy. In: E Marré, M Tostand, H-J Zenker, eds. *Normal and pathologic colour vision*. Halle: Martin Luther University, 1987: 53-9.
- 15 Bresnick GH, Smith VC, Pokorny J. Autosomal dominantly inherited macular dystrophy with preferential short-wavelength sensitive cone involvement. *Am J Ophthalmol* 1989; 108: 265-76.
- 16 Nathans J, Piantanida TP, Eddy RL, Shows TB, Hogness DS. Molecular genetics of inherited variation in human color vision. *Science* 1986; 232: 203-10.

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- REFERENCES:** 1. Jones H, Ekberg NL. Letter N Eng J Med 1979; **301**: 270.
2. Levy NS, Boone L, Ellis E. Glaucoma 1985; **7**: 54-62.
3. Schoene RB, Abuan T, Ward RL, Beasley CH. Am J Ophthalmol 1984; **97**: 86-92.
4. Van Buskirk EM. New Trends in Ophthalmol 1986; **104**: 1178-1184.

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Use of orbital floor steroids in the management of patients with uniocular non-necrotising scleritis

K N Hakin, J Ham, S L Lightman

Abstract

Most cases of non-necrotising scleritis can be successfully treated with non-steroidal anti-inflammatory drugs. If these are ineffective, then high-dose systemic corticosteroids, with all their attendant side-effects, are usually required. We have used orbital floor injections of depot steroid in the management of nine patients with non-necrotising scleritis in an attempt to avoid the use of systemic steroids, or to allow the dose of steroids to be reduced while maintaining disease control. A temporary reduction in inflammation was achieved in all cases, which allowed the use of systemic steroids to be avoided altogether in two patients and delayed in the others. Non-steroidal anti-inflammatory drugs and systemic corticosteroids remain the mainstay of treatment for non-necrotising scleritis, but orbital floor injections may be a useful adjunct in certain cases.

Scleritis is a potentially serious disorder, which can occur in both young and old patients. Although it can be associated with an underlying collagen disease, many patients are healthy. Pain is a predominant feature of active scleral inflammation, and is the usual presenting complaint.

Patients with anterior diffuse (Fig 1) or nodular, non-necrotising scleritis, and posterior scleritis, can often be treated with non-steroidal anti-inflammatory drugs (NSAIDs), such as flurbiprofen or indomethacin. Necrotising scleritis, however, always requires systemic steroid therapy, sometimes in combination with other systemic immunosuppressive drugs.¹ Topical steroid therapy can control episcleral inflammation but has no effect on scleral inflammation. Subconjunctival steroid injections are contraindicated because of the risk of scleral thinning and perforation.²

Some patients with non-necrotising disease do not respond to non-steroidal therapy and require systemic corticosteroids for disease control. As

with intraocular inflammation, high doses (prednisolone 40-80 mg per day) may be required. Many patients with uniocular posterior uveitis, however, are spared the problems associated with systemic steroid therapy by the use of orbital floor sub-Tenon's injection of depot steroid preparations when there is active inflammation.³ This route of treatment is particularly useful in patients with unilateral disease who are otherwise healthy. It is also useful in maintaining control of a unilateral exacerbation of disease while on a reducing regimen of systemic steroids.

In this study we aimed to see if patients with uniocular non-necrotising scleral inflammation in whom NSAIDs were ineffective, or could not be tolerated, could be treated with orbital floor injections of long-acting depot steroid preparations. We also treated three patients in whom the disease process had relapsed while on a reducing regimen of systemic steroids, in order to avoid returning to a high steroid dosage.

Patients and methods

Patients were recruited from the Scleritis Clinic at Moorfields Eye Hospital. The scleritis was classified as either anterior or posterior, and diffuse, nodular, or necrotising.¹ Investigations were performed to exclude an underlying systemic disease process.

All patients with necrotising disease were treated with high-dose systemic corticosteroids (prednisolone 60-80 mg per day), together with other immunosuppressive therapy if required. All patients with anterior diffuse or nodular, or posterior, scleritis were initially treated with flurbiprofen 100 mg three times a day, unless this previously could not be tolerated or had been found to be ineffective, in which case systemic steroids were started. Oral H₂ receptor antagonists were given concurrently to patients with a previous history of peptic ulceration or indigestion.

After one or two weeks of treatment the patients were reassessed. If the pain was controlled, and the degree of inflammation reduced, the NSAIDs were continued, and eventually tapered off when the disease process was quiescent. If there was no change, or if the inflammation had increased, then systemic steroids were started in cases of bilateral disease. Patients with unilateral disease, however, received, with informed consent, an orbital floor injection of 40 mg methylprednisolone acetate (Depomedrone). The steroid was mixed with 0.2 ml lignocaine 2%, and administered through the lower lid, at the junction of the inner two-thirds and outer one-third.⁴ The patients were examined again after one or two weeks, and



Figure 1 Anterior diffuse scleritis.

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Table 1 Results

Patient no	Age/sex	Diagnosis	Indication for depot injection	Duration of effect	Delay achieved before use of high-dose steroids
1	66/F	Nodular	NSAID hypersensitivity	4 days	2 weeks
2	50/M	Nodular	NSAID intolerance	Symptom relief; signs unchanged	Steroids not required
3	24/F	Posterior	NSAID ineffective	1 week	2 weeks
4	65/M	Nodular	Relapse on flurbiprofen, prednisolone 10 mg	5 days	2 weeks
5	48/F	Posterior	Relapse when prednisolone <20 mg	Allowed steroid reduction for 5 weeks	6 weeks
6	63/F	Diffuse	Severe steroid side effects	2 weeks	5 months (3 injections)
7	37/F	Nodular	Relapse when prednisolone <20 mg	3 months	9 months
8	89/F	Diffuse	Relapse on prednisolone 5 mg	3 months	No increase required
9	64/F	Posterior	Relapse on prednisolone 5 mg	4 weeks	4 weeks (injection repeated for further relapse at 8 months to allow blood pressure control)

subsequently at intervals determined by the disease activity. Additional treatment, including repeat injections, was administered as required. If an injection was repeated within several weeks, shorter acting methylprednisolone succinate (Solumedrone) was used instead of Depomedrone to avoid build-up of high levels of depot steroid beneath the globe.

Results

All patients included in this trial had non-necrotising, anterior diffuse or nodular, or posterior scleritis, active in one eye only. No underlying disease process was detected in any patient.

The results are displayed in Table 1. Nine patients received an orbital floor steroid injection. They could be divided into two groups: group A (patients 1-3) in whom NSAIDs were ineffective or could not be tolerated, and in whom systemic steroids had not yet been used; group B (patients 4-9) in whom systemic steroids had been previously used with good effect, but recourse to a high dose was now to be avoided. Seven patients received one injection, one received two, and another three.

In group A the treatment achieved pain control for only four days in one patient and seven days in another. Both required subsequent high-dose systemic steroid therapy to control the scleral inflammation, instituted two weeks after injection. In the third, although pain was controlled, a large scleral nodule remained unaffected. No steroids were required in this patient, however, as there was now no active inflammation.

In group B only one patient (no. 8) did not require an increase of systemic steroids to achieve disease control eventually. The use of high-dose steroids, however, was delayed for five months in one patient and nine months in another. In patient nine the use of orbital floor steroids allowed a dangerously high blood pressure to be satisfactorily controlled before oral steroids were started.

There were no complications from the procedure, which was generally well tolerated by the patient.

Discussion

This study has demonstrated a limited role for orbital floor steroid in the management of non-

necrotising scleritis. Although the local steroid does exert some anti-inflammatory action, this tends to be short-lived. Systemic NSAIDs, particularly flurbiprofen and indomethacin, are well established as the first-line treatment of non-necrotising scleritis.¹ Necrotising scleritis, however, always requires high-dose systemic corticosteroids, sometimes with additional immunosuppressives such as cyclophosphamide and azathioprine.⁵ Systemic steroids are also used in cases of non-necrotising disease which do not respond to NSAIDs. Although they are generally very effective at controlling scleral inflammation, their use is associated with many side effects which can preclude their use. 'Pulse' steroid therapy has been used to try to reduce these side effects^{6,7} and more recently cyclosporin A.⁸

Patients with uniocular intraocular inflammation have long been spared treatment with systemic steroids by the administration of orbital floor depot steroid preparations. Watson and Hayreh⁹ have stated that intraorbital steroid injections have only a transient effect with scleritis, and that frequent injections are required for disease control. Benson,¹⁰ however, states that in posterior scleritis retrobulbar steroids can be effective and without complications.

It is always desirable to minimise, or avoid altogether, the use of systemic steroids, in the management of non-necrotising scleritis. Mondino and Phinney,¹¹ reporting on six patients with non-necrotising scleritis who were not satisfactorily controlled on either NSAIDs or steroid alone, managed to reduce the dose of controlling systemic corticosteroid by combining prednisolone with oral indomethacin. We have reported on five patients with non-necrotising disease in whom the concurrent use of cyclosporin A allowed the reduction of systemic steroids without relapse.¹² In this study the use of orbital floor steroids allowed systemic steroids to be avoided altogether in one patient, to be maintained at a low dose of 5 mg in another, and delayed the progress of disease in two others. Perhaps the most important function was in tiding over a patient, whose high blood pressure presented a positive contraindication to the administration of high-dose steroids, until the blood pressure could be reduced.

NSAIDs remain the initial therapy for non-necrotising scleritis, followed by systemic steroids should the NSAIDs prove to be ineffec-

tive. If the use of steroids is temporarily contraindicated, however, or should it prove to be difficult to reduce the minimum controlling steroid dose, then orbital floor steroid should be considered as a useful adjunct.

- 1 Watson PG. The nature and treatment of scleral inflammation. *Trans Ophthalmol Soc UK* 1982; 102: 257-81.
- 2 Watson PG. Diseases of the sclera. In: Duane TD, ed. *Clinical ophthalmology*. Hagerstown: Harper and Row, 1984; 4: chapter 23: 10-27.
- 3 Jennings T, Rusin MM, Tessler HH, Cunha-Vaz JG. Posterior sub-Tenon's injections of corticosteroids in uveitis patients with cystoid macular edema. *Jpn J Ophthalmol* 1988; 32: 385-91.
- 4 Tessler HH. Uveitis. In: Peyman GA, Sanders DR, Goldberg MF, eds. *Principles and practice of ophthalmology*. 1st ed. Philadelphia: Saunders, 1980; 2: 1554-632.
- 5 Foster CS. Immunosuppressive therapy for external ocular inflammatory disease. *Ophthalmology* 1980; 87: 140-50.
- 6 McCluskey P, Wakefield D. Intravenous pulse methylprednisolone in scleritis. *Arch Ophthalmol* 1985; 105: 793-7.
- 7 Meyer PAR, Watson PG, Franks W, Dubord P. 'Pulsed' immunosuppressive therapy in the treatment of immunologically induced corneal and scleral disease. *Eye* 1987; 1: 487-95.
- 8 Wakefield D, McCluskey P. Cyclosporin therapy for severe scleritis. *Br J Ophthalmol* 1989; 73: 743-6.
- 9 Watson PG, Hayreh SS. Scleritis and episcleritis. *Br J Ophthalmol* 1976; 60: 163-91.
- 10 Benson WE. Posterior scleritis. *Surv Ophthalmol* 1988; 32: 297-316.
- 11 Mondino BJ, Phinney RB. Treatment of scleritis with combined oral prednisone and indomethacin therapy. *Am J Ophthalmol* 1988; 106: 473-9.
- 12 Hakin KN, Ham J, Lightman SL. Use of cyclosporin in the management of steroid dependent non-necrotising scleritis. *Br J Ophthalmol* 1991; 75: 340-1.

Use of cyclosporin in the management of steroid dependent non-necrotising scleritis

K N Hakin, J Ham, S L Lightman

Abstract

Many patients with non-necrotising scleritis can be treated adequately with non-steroidal anti-inflammatory drugs or steroids. But, as many of them are young, treatment may present problems if they require high doses of steroids to control the scleral inflammation and then relapse when the dosage is reduced. Five such patients were treated with a combination of steroids and low-dose cyclosporin therapy, and in all cases the scleritis remained under control on a much lower dose of steroids than when steroids were used alone. Cyclosporin is therefore a useful drug in the management of younger patients dependent on high-dose steroids to control their scleral inflammation.

Anterior scleritis can be diffuse, nodular, or necrotising.¹ In many patients non-steroidal anti-inflammatory drugs (NSAIDs), such as flurbiprofen, can be used to control diffuse or nodular scleritis, whereas high-dose steroids, often with other potent immunosuppressives such as cyclophosphamide, are necessary for the treatment of necrotising scleritis.²

Cyclosporin, which is used extensively in the treatment of posterior uveitis, has previously been described in the treatment of necrotising disease, which usually occurs in older patients.³

We here present five patients with severe anterior diffuse scleritis in whom systemic prednisolone was effective only at high dosage or could not be tolerated at such doses. Any attempt at steroid reduction resulted in severe recurrence of the scleral inflammation. These patients received low-dose cyclosporin (5 mg/kg/day) in addition to the controlling steroid dose, and in all cases the steroid dosage could then be reduced to a more acceptable level while the scleral inflammation remained under control.

Patients and methods

The patients were recruited from the Scleritis Clinic at Moorfields Eye Hospital. The scleritis was classified as anterior diffuse, nodular or necrotising, or posterior, according to Watson.¹ Investigations including a full blood count, erythrocyte sedimentation rate, autoimmune screen, urea, electrolytes, creatinine, and chest x ray were performed to exclude an underlying systemic disease.

Patients with non-necrotising disease were started on an NSAID, usually flurbiprofen or indomethacin, which if ineffective, was then changed to high-dose systemic corticosteroid, prednisolone 60-80 mg per day. After one or two weeks at this high level a slow reduction of the daily dose was attempted, eventually to be

stopped completely. If the disease relapsed as the steroids were reduced, then NSAID were sometimes combined with the steroids to attempt disease control. If the inflammation could not be controlled on a satisfactorily low steroid level, the steroids were increased back to or above the controlling dose, and cyclosporin A added, at 5 mg/kg/day, in two divided doses, after the serum creatinine was checked and found to be within the normal range. After one or two weeks on the combination therapy slow steroid reduction was attempted.

The cyclosporin dose was monitored by two-weekly serum creatinine measurements and adjusted if the creatinine started to rise. If relapse occurred while treatment was being reduced, the prednisolone dose was increased and then again slowly tapered off. The cyclosporin was also increased, if thought necessary, but to a maximum dose of 7.5 mg/kg/day for up to a week, before being reduced back to 5 mg/kg/day.

Results

Five patients with non-necrotising scleritis received cyclosporin. Their ages ranged from 21 to 64 years, average 32. Systemic investigations revealed Crohn's disease with primary sclerosing cholangitis in one patient and nasal cartilage collapse in another (possibly indicative of relapsing polychondritis). The others were healthy. In four patients satisfactory control of the ocular inflammation was achieved with high-dose steroids, but the disease relapsed when the treatment was reduced. The ocular inflammation was said to be controlled when the patient no longer experienced pain and the slit-lamp examination showed resolution of oedema, with minimal dilatation of the episcleral vessels. The fifth patient immediately developed intolerable side effects from the steroids, and thus required alternative therapy. Four received NSAID/steroid combination therapy to try to control the relapses, and one of these was also treated with azathioprine.

In all five patients the concurrent use of cyclosporin with prednisolone allowed the daily dose of prednisolone to be reduced. Three patients did relapse again (one on three occasions) but are now well controlled on a low daily steroid dose after the steroid dose had been temporarily increased to greater than 40 mg/day to re-establish control. Two patients managed to stop all treatment, one after seven weeks, the other after eight months, of cyclosporin therapy. There were no detectable renal complications from the use of cyclosporin as judged by the serum creatinine. Hirsutism, in one patient, was the only side effect.

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Table 1 Results

Age/ sex	Diagnosis	Duration of disease	Previous treatment	Minimum steroid prior to cyclosporin	Duration of cyclosporin treatment	Relapse?	Current therapy
64/M	Ant.scleritis/ limbitis	5 months	Flurbiprofen/pred	Pred 25 mg	6 months	Yes	Cyclosporin 200 mg/ pred 10 mg
23/F	Ant.scleritis	4 years	Flurbiprofen/pred	Side effects at pred 50 mg	18 months	Yes	Cyclosporin 200 mg/ pred 5 mg Flurbiprofen
28/M	Ant.scleritis	1 month	Indomethacin/pred	Pred 15 mg	7 weeks	No	Nil
21/F	Post.uveitis/ scleritis	6 years	Indomethacin/pred/ azathioprine	Pred 35 mg	13 months	Yes	Cyclosporin 150 mg/ pred 10 mg
26/M	Ant.scleritis	5 months	Flurbiprofen/pred	Pred 40 mg	8 months	No	Nil

Pred=prednisolone.

Discussion

Many patients with non-necrotising scleral disease can be controlled with systemic NSAIDs. Some require systemic steroids for control of the scleral inflammation (as judged by decreased pain and redness), and with slow steroid reduction many experience continued control of the disease on low-dose therapy. A minority require high-dose steroid therapy, and their disease process can become very steroid sensitive, so that any attempt at dose reduction results in relapse. The use of immunosuppressive drugs such as cyclophosphamide and chlorambucil is contraindicated in young patients,⁴ and in many patients with scleritis we have found azathioprine to be of little use in the short term in allowing significant steroid reduction.

Cyclosporin is now commonly used together with steroids in the management of posterior uveitis.^{5,6} Control of the disease is achieved with a lower dose of steroid than with steroids alone. In younger patients side effects such as tremor, hirsutism, gingival hypertrophy, and renal damage appear to be less common and the drug generally well tolerated.

Low-dose cyclosporin (less than 7.5 mg/kg/day) is now used, as at the higher dose of 10 mg/kg/day renal toxicity is common.⁷ At this lower dose cyclosporin must be used in combination with steroids to be effective in controlling the disease. The steroid dose may then be slowly reduced while the scleral disease is closely monitored.

Wakefield and McCluskey³ reported that cyclo-

sporin was a useful additional drug in the management of necrotising scleral disease. We have found that in combination with steroids it is also useful in treating non-necrotising disease, having a steroid-sparing effect.

Cyclosporin works by selectively inhibiting lymphokine secretion by activated T cells. Little is known about the pathogenesis of scleral inflammation, but a granulomatous inflammatory process is seen histologically.^{8,9} T lymphocytes, particularly of the CD4+ subtype, are involved in the delayed hypersensitivity response and may be involved in the inflammatory process in the sclera. The fact that cyclosporin is effective in the disease suggests that T cells are involved in the pathogenesis of the scleral inflammation, and this is under further investigation.

- 1 Watson PG. The nature and treatment of scleral inflammation. *Trans Ophthalmol Soc UK* 1982; 102: 257-81.
- 2 Foster CS. Immunosuppressive therapy for external ocular inflammatory disease. *Ophthalmology* 1980; 87: 140-50.
- 3 Wakefield D, McCluskey P. Cyclosporin therapy for severe scleritis. *Br J Ophthalmol* 1989; 73: 743-6.
- 4 Tabbara KF. Chlorambucil in Behçet's disease: a reappraisal. *Ophthalmology* 1983; 90: 906-8.
- 5 Nussenblatt RB, Palestine AG, Rook AH. Treatment of intraocular inflammatory disease with cyclosporin A. *Lancet* 1983; ii: 235-8.
- 6 Towler HMA, Whiting PH, Forrester JV. Combination low-dose cyclosporin A and steroid therapy in chronic intraocular inflammation. *Eye* 1990; 4: 514-20.
- 7 Palestine AG, Austin AH III, Barlow JE, et al. Renal histopathological alterations in patients treated with cyclosporin for uveitis. *N Engl J Med* 1986; 314: 1293-8.
- 8 Sevel D. Necrogranulomatous keratitis associated with Wegener's granulomatosis and rheumatoid arthritis. *Am J Ophthalmol* 1967; 63: 250-5.
- 9 Young RD, Watson PG. Microscopical studies of necrotising scleritis: I. Cellular aspects. *Br J Ophthalmol* 1984; 770-8.

Conjunctival cysts in anophthalmic orbits

Ton J Smit, Leo Koornneef, Frans W Zonneveld

Abstract

Five out of 149 patients (3%) who received an intraorbital implant to prevent or treat the disfiguring symptoms associated with the postenucleation socket syndrome developed intraorbital conjunctival cysts. All five patients had received a secondary implant two to 14 months previously. After excision of the cysts four patients required additional surgery for lack of conjunctiva and/or recurrent cyst formation. The clinical findings, mechanism of development, and management of this rare but serious complication of socket surgery are described.

Conjunctival cysts of the orbit following enucleation are rare. Only 17 cases of orbital conjunctival cyst formation after enucleation have been reported.¹⁻⁶ We have seen this complication in five patients over a period of seven years.

Patients and methods

The patients consisted of 149 patients referred to the Orbital Center who received an intraorbital implant between January 1982 and April 1989 to prevent or treat the disfiguring symptoms associated with the postenucleation socket syndrome. Fifty-one patients had the implant placed at the time of enucleation (primary implant), 73 some time after enucleation (secondary implant), 17 after replacement of a previously inserted inadequate implant, and eight after an evisceration of the eye. The implants were 18 mm acrylic balls covered with donor sclera, the so-called baseball implants.⁷ For patients whose eyes were eviscerated 18 mm bare acrylic balls were used. The implants were inserted in a standardised manner.^{6,8}

Results

Five patients in this series, all with a secondary implant, developed conjunctival cysts in the anophthalmic orbit two to 14 months after the implantation of the baseball (Table 1). In all five increasing difficulty in retaining the prosthesis was the first sign. Proptosis of the prosthesis and shallowness of the fornices (the inferior fornix in four, the superior fornix in one) was also noted. In two a palpable mass was found.



Figure 1 Sagittal CT scan of the anophthalmic orbit (patient 3). A large conjunctival cyst superior to the implant is present. The implant is displaced downwards.

Diagnosis was established with high resolution computerised tomography (CT) in two patients (Fig 1) and with fine needle aspiration of 6-7 ml of a yellow-grey fluid from the mass in one patient. In the other two patients the cysts were accidentally found during surgery for deepening the fornix. In three of the five patients multiple cysts were present. Complete excision was undertaken in all cases.

During excision three implants were replaced because they appeared to communicate with the cysts. The two patients in whom the implant was not replaced at first had a recurrence. The recurrent cysts were removed completely in a second session, together with the implant in one patient. So altogether four out of five implants had to be replaced. In three patients a donor sclera-covered ball was reinserted; in one patient a dermis fat graft was used after recurrent cyst excision because this patient also showed lack of conjunctiva (Table 2).

Histopathological examination revealed cysts lined with non-keratinising stratified squamous epithelium and surrounded by fibrous tissue.

Lack of conjunctiva, resulting in shallow fornices, was a complication found in three patients after excision of the cysts. This required additional treatment: two patients had fornix reconstruction with oral mucous membrane grafts, and in one patient a dermis fat implant was placed instead of a baseball implant - and later on a mucous membrane graft (Table 2).

Unfortunately, the final cosmetic result was poor in all five patients.

Discussion

Orbital cyst formation following enucleation is a

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Table 1 Patient data

Patient no.	Age at enucleation (years)	Age at implantation (years)	Age at cyst excision (years)	Time interval from enucleation to cyst excision (years)	Time interval from implantation to cyst excision (months)
1	18	33	33	15	2
2	0.5	53	54	53	14
3	8	31	31	23	4
4	22	39	40	18	14
5	2	30	30	28	3

Table 2 Clinical details

Patient no.	Reason for enucleation	Surgery	Multiple cysts	Additional surgery
1	Trauma	Excision cyst	–	Recurrent cyst excision, replacement implant with dermis fat graft, mucous membrane graft
2	Retinoblastoma	Excision cyst, replacement implant	–	Mucous membrane graft
3	Glioma	Excision cysts	+	Recurrent cyst excision
4	Trauma	Excision cysts, replacement implant	+	Mucous membrane graft
5	Melanoma	Excision cysts, replacement implant	+	

rare but serious complication. In our population it was found in 3% of the patients, but only in those in whom a secondary implant was inserted. Tyers and Collin⁶ found conjunctival implantation cysts in 7% of a series of six primary and 35 secondary implantations. They did not describe whether the cysts were found in the primary or in the secondary implant group. They appeared to consider these cysts to be of minor importance, because they could be removed easily, with direct closure of conjunctiva, owing to their being so close to the conjunctival surface.

In our series, however, it appeared to be a serious complication because of the need for further surgery in four of the five patients after excision of the cyst(s). The surgical measures in all five patients, consisting in removal of the cysts and surgical treatment of the subsequent complications, led to deterioration of the cosmetic outcome.

McCarthy *et al*³ postulated three possible mechanisms for the development of conjunctival cysts in an anophthalmic orbit: (1) inadvertent implantation of a free fragment of conjunctiva within Tenon's capsule during enucleation surgery; (2) incarceration of a tongue of conjunctiva that is accidentally inverted in wound closure through Tenon's capsule; (3) epithelial downgrowth by wound dehiscence. The viable

conjunctiva buried in the socket by one of these mechanisms may form the orbital conjunctival cyst.

It is therefore not surprising that in our series conjunctival cysts were found only in patients with a secondary implant. In contrast to a primary implantation, the orbital anatomy in secondary implantations has already been disturbed, and a space for the implant has to be created by sharp dissection inside the collapsed orbital tissues. Because of this the secondary implantation technique is more complicated. The risk of implantation of conjunctiva into the orbit is increased, because accurate closure of Tenon's capsule and conjunctiva is more difficult. It is therefore important to close Tenon's capsule and conjunctiva with great care in two separate layers. If conjunctival cysts still develop, it is better to remove the implant as well to forestall further recurrences.

We conclude that orbital cyst formation is rare in patients with a primary implant. If orbital conjunctival cysts occur in secondary implants, we recommend removal of the implant together with the cysts to prevent further complications. In general the final cosmetic outcome in these patients remains poor.

1 Allison SC, Wergeland FL. Giant conjunctival cyst of the orbit. *Ann Ophthalmol* 1973; 5: 199–202.
2 Judisch GF, Maumenee IH. Large orbital conjunctival cyst after enucleation. *Am J Ophthalmol* 1977; 83: 49–51.
3 McCarthy RW, Beyer CK, Dallow RL, Burke JF, Lessell S. Conjunctival cysts of the orbit following enucleation. *Ophthalmology* 1981; 88: 30–5.
4 Hornblass A, Bosniak S. Orbital cysts following enucleation: the use of absolute alcohol. *Ophthalmic Surg* 1981; 12: 123–6.
5 Thach AB, Busack JA, La Piana FG. Orbital cyst with pseudooptic nerve: CT features. *J Comput Assist Tomogr* 1990; 14: 131–2.
6 Tyers AG, Collin JRO. Baseball orbital implants: a review of 39 patients. *Br J Ophthalmol* 1985; 69: 438–42.
7 Frueh BR, Felker GV. Baseball implant. A method of secondary insertion of an intraorbital implant. *Arch Ophthalmol* 1976; 94: 429–30.
8 Collin JRO. Socket surgery. In: Collin JRO, ed. *A manual of systematic eyelid surgery*. Edinburgh: Churchill Livingstone, 1989: 121–37.

Lid lengthening by sclera interposition for eyelid retraction in Graves' ophthalmopathy

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Abstract

The efficacy of scleral grafts for eyelid lengthening in patients with thyroid related upper and/or lower lid retraction was evaluated in 62 consecutive patients with Graves' ophthalmopathy who underwent lid surgery in the last 3.5 years. Seventy-eight upper and 30 lower lids were lengthened by scleral interposition. A good or acceptable result was achieved in 50% of all operated upper lids after one procedure. This percentage increased to 75% after a second and to 77% after a third procedure. Persistent temporal retraction and nasal overcorrection were the major complications. In lower lid lengthening the success percentage was 90% after one operation. We conclude that scleral grafting for upper eyelid lengthening has no distinct advantage in comparison with other lengthening techniques. Scleral implants to lengthen lower lids are very effective.

Even after successful treatment with corticosteroids or orbital irradiation many patients with Graves' ophthalmopathy need surgical repair for rehabilitation. This may yield excellent results provided surgery is deferred till ocular and orbital symptoms have become stable.¹ Disfiguring proptosis can be treated by orbital decompression, while the field of binocular single vision can be restored by extraocular muscle surgery.^{2,3} Eyelid lengthening with or without dermatochalasis correction is usually the final step of surgical rehabilitation.

Many different techniques have been described to lengthen eyelids in Graves' ophthalmopathy. In 1979 Callahan and Callahan stated that recession of the eyelid retractors is best achieved with scleral grafts.⁴ Indeed the use of sclera for lower lid lengthening has been generally accepted. However, there is disagreement about its use in the treatment of thyroid related upper lid retraction. For this condition sclera has been advocated by some,^{5,6} while its efficacy has been questioned by others.⁷⁻⁹ Unfortunately, sufficient data on surgical outcome are lacking in most of these studies.

We report on a large series of consecutive patients in whom sclera has been used for both upper and lower lid lengthening. The outcome of our treatment method is compared with that of other methods.

Patients and methods

From January 1986 till July 1989 62 consecutive patients with thyroid related eyelid retraction underwent lid lengthening by scleral interposition at the Orbital Centre of Amsterdam.

Table 1 Patient's characteristics

	Upper lid lengthening	Lower lid lengthening
No. of patients	47	22
No. of eyelids	78	30
Female/male ratio	4:1	2:1
Mean age and range (yr): M	47 (26-64)	48 (29-60)
F	55 (48-68)	56 (42-68)

Seventy-eight upper and 30 lower lids were corrected. Information on the patients is summarised in Table 1.

The diagnosis of Graves' ophthalmopathy was based on clinical signs and symptoms and coronal CT scans of the orbit. All patients were euthyroid and had stable eye disease for at least half a year prior to lid surgery. Many patients had been treated with immunosuppressive treatment, radiotherapy, orbital decompression, and extraocular muscle surgery.

The indication for surgical correction was cosmesis in all patients, but the majority complained of ocular discomfort as well, and luxation of the globe was imminent in two.

Preoperative evaluation consisted in measurements of palpebral fissure and scleral show in the primary position of gaze at 12 and 6 o'clock, lid margin to lid crease distance definition, and exophthalmometer readings. Pre- and post-operative photographs were taken of all patients.

The outcome of surgery was evaluated after three months. Second and third procedures were performed if no cosmetically acceptable result had been achieved. The final cosmetic result was evaluated by the patients and the surgeons. Upper lid correction was considered to be good if (1) the upper 1.5 to 2.0 mm of the cornea at the 12 o'clock position was covered by the lid; (2) the lid margin contour was smooth; (3) the lid crease was within 7 to 10 mm of the lid margin; and (4) there was bilateral symmetry (Figs 1 and 2A, B). An acceptable result was considered to be 1 to 2 mm over or under correction or mild asymmetry, requiring no further surgery (Figs 3A, B). If the lid margin of the lower lid touched the limbus at the 6 o'clock position and the contour was smooth, lower lid correction was considered to be good (Figs 4A, B). When there was a gap between the lid and the limbus of no more than 1 mm, it was considered acceptable.

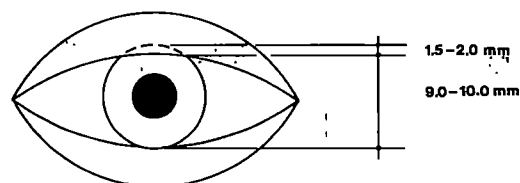


Figure 1 Drawing showing contour and position of eyelids in ideal situation.

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Figure 2 Pre- and postoperative appearance of a patient with unilateral upper eyelid retraction. Good result.



Figure 2A.



Figure 2B.

Figure 3 Pre- and postoperative appearance of a patient with unilateral upper eyelid retraction. Slight asymmetry, acceptable result.



Figure 3A.



Figure 3B.

Figure 4 Pre- and postoperative appearance of a patient with unilateral, left-sided lower lid retraction. Good result.



Figure 4A.



Figure 4B.

SURGICAL TECHNIQUE

The approach is much as described for ptosis surgery previously.¹⁰ A horizontal line is drawn on the eyelid at about 7 mm from the lid margin to mark the place of the future skin crease. After eversion of the superior eyelid, 2 ml of lignocaine 2% with epinephrine is injected into the subconjunctival area. Thus the conjunctiva is separated from Müller's muscle. The upper eyelid is then further anaesthetised subcutaneously with approximately 3 ml of local anaesthetic. A horizontal incision in the skin crease is made through the skin-muscle layer parallel to the muscle fibres on to the tarsal plate. By going upward in the direction of the upper roof of the orbit the orbital septum is visualised. The septum is opened, the orbital fat is freed, and below the fat the levator aponeurosis is identified. The levator aponeurosis together with Müller's muscle are dissected off the tarsal plate, and the medial and lateral horns are transected. The conjunctiva, however, is left unimpaired, thus protecting the cornea. Special care is taken to cut all fibrotic strands in the lacrimal gland region. A scleral graft is sutured to the tarsal plate and the levator muscle with interrupted 5-0 Vicryl sutures. In upper lids the vertical height of the implant is approximately twice the amount of eyelid retraction, laterally some millimetres more than medially. However, the final determination of the levator recession and thus of the graft size is based on the operation table appearance of the lid margin. For

these assessments the patient is asked to open and close his eyes. When the result is satisfactory, the skin is closed with 6-0 silk sutures.

In second and third procedures the eyelid is opened up through the former scar. The scleral implant is dissected free and adjusted or replaced.

In lower lids the approach is transconjunctival. After infiltration of the subconjunctival space with local anaesthetic the conjunctiva is incised over the lower border of the tarsal plate. The lower lid retractors are identified and dissected off the conjunctiva and the tarsus and freed of the orbital septum. A scleral graft of about three times the lid retraction in millimetres is sutured to the retractors and the tarsal plate with 5-0 Vycril. The conjunctiva is closed with a running 6-0 catgut suture.

Results

The outcome of surgery was evaluated at a fixed interval three months postoperatively. Follow-up varied from 0.5 to 3.5 years. The results of upper lid lengthening are given in Table 2 and Fig 5. Less retraction postoperatively was seen in all patients, and ocular discomfort disappeared in all but two. The cosmetic result was good or acceptable in 50% after one procedure and in 77% after a maximum of three procedures. Final evaluation showed mild or severe overcorrection or medial dropping in seven lids and temporal

Table 2 Final outcome of upper lid lengthening procedures by sclera implantation for thyroid related eyelid retraction

Amount of retraction	Number	Result			
		Success			Failure
		Good	Acceptable	Total	
1-3 mm	25	20%	52%	72%	28%
4-5 mm	36	33%	53%	86%	14%
6-10 mm	17	18%	47%	65%	35%
1-10 mm	78	26%	51%	77%	23%

obliquity in another seven lids (Figs 6A, B). Asymmetry was seen in four patients, and a thickened eyelid for longer than one month in two. Other complications such as a dry eye, loss of lashes, or extrusion of the graft did not occur. No recurrence of retraction was seen in this group.

The results of lower lid lengthening are given in Table 3 and Figs 7A, B. After one operation all but three patients had a good or acceptable result. Within a year, a recurrence of retraction was noted in two patients.

Discussion

The difficulty of surgical correction of upper lid retraction in Graves' ophthalmopathy is illustrated by the numerous procedures described to recess the lid retractors. Henderson's müllerotomy is insufficient to obtain enough recession in most patients.^{9,11} Groves's levator marginal myotomy¹² tends to lead to unpredictable results. His own series was too small to draw conclusions from. Several other techniques¹³⁻¹⁵ have not been analysed in large enough numbers to demonstrate a high rate of success.

We have used scleral grafts to lengthen upper and lower lids in patients with Graves' ophthalmopathy because we expected more predictable and favourable results. After one procedure, however, only 50% of all operated upper lids were satisfactory. It has been suggested that scleral grafts cause lid thickening, cysts, and corneal damage,¹⁶ but in our patients (medial) overcorrection and/or obliquity of the lid edge as a result of persistent temporal retraction were the most important complications. Meticulous dissection of the lateral part of the levator aponeurosis could not prevent this. To avoid persistent temporal retraction we have used grafts that were so tapered they were wider temporally than medially, as suggested by Dryden and Soll.⁵ In spite of this, temporal retraction was noted even after a second and



Figure 6A.



Figure 6B.

Figure 6 Pre- and postoperative appearance of a patient with bilateral upper eyelid retraction. Typical persistent temporal retraction with resulting oblique lid edge. Unacceptable result.

third procedure. In these patients we found considerable fibrosis in the lacrimal gland region, which tended to recur after repeated procedures. We suggest that this excessive fibrosis may be caused by the scleral implant.

Despite the fact that Putterman defined his criteria for success of lid surgery in less detail, he appears to have excellent results from a graded Müller's muscle excision and levator recession without the use of sclera: 80% of his 32 patients had a satisfactory result after one intervention.^{7,17} Thaller *et al* also reported good results in two-thirds of 30 patients after levator recession without the use of sclera. Levator recession with scleral graft in their hands was less predictable.⁹

Although it is impossible to make a statistical comparison between their procedures and our method, these reports and our experience with scleral grafts indicate that sclera does not in-

Table 3 Final outcome of lower lid lengthening procedures by sclera implantation for thyroid related eyelid retraction

Number	Result			
	Success			Failure
	Good	Acceptable	Total	
30	63%	34%	97%	3%

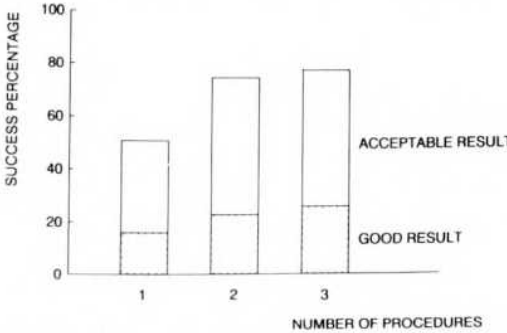


Figure 5 Diagram showing success percentage of upper lid lengthening in relation to number of procedures.

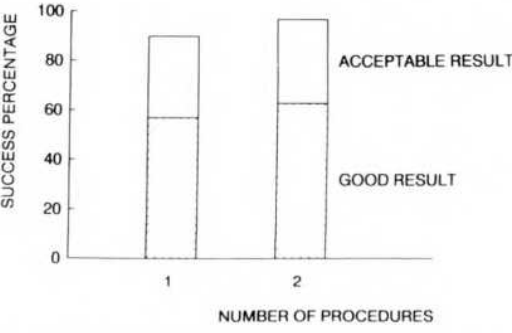


Figure 7 Diagram showing success percentage of lower lid lengthening in relation to number of procedures.

crease the success rate of upper lid lengthening. On the other hand, our data do not prove that lid lengthening with sclera yields less acceptable results. We believe that, until it has been demonstrated that the more difficult procedure has a higher success rate, the simpler method should be the one of choice. For this reason we do not recommend scleral grafts for upper lid lengthening in Graves' ophthalmopathy.

Sclera for lower lid lengthening, on the contrary, is known to support the lid as a semi-stiff spacer against gravity.⁹ This might explain our satisfactory results in lower lid surgery.

- 1 Mourits MP, Koornneef L, Wiersinga WM, Prummel MF, Bergbom A, van der Gaag R. Clinical criteria for the assessment of disease activity in Graves' ophthalmopathy: a novel approach. *Br J Ophthalmol* 1989; 73: 639-44.
- 2 Mourits MP, Koornneef L, Wiersinga WM, Prummel MF, Bergbom A, van der Gaag R. Orbital decompression for Graves' ophthalmopathy by inferomedial, by inferomedial plus lateral, and by coronal approach. *Ophthalmology* 1990; 97: 636-41.
- 3 Mourits MP, Koornneef L, van Mourik-Noordenbos, et al. Extraocular muscle surgery for Graves' ophthalmopathy. Does prior treatment influence surgical outcome? *Br J Ophthalmol* 1990; 74: 481-3.
- 4 Callahan MA, Callahan A. Surgery for endocrine ophthalmopathy. In: Callahan MA, Callahan A, eds. *Ophthalmic plastic and orbital surgery*. Alabama: Aesculapius, 1979: 146.
- 5 Dryden RM, Soll DB. The use of scleral transplantation in cicatricial entropion and eyelid retraction. *Ophthalmology* 1977; 83: OP669-78.
- 6 Doxanas MT, Dryden RM. The use of sclera in the treatment of dysthyroid eyelid retraction. *Ophthalmology* 1981; 88: 887-94.
- 7 Putterman AM. Surgical treatment of thyroid-related upper eyelid retraction. Graded Müller's muscle excision and levator recession. *Ophthalmology* 1981; 88: 507-12.
- 8 Waller RR, Samples JR, Yeatts RP. Eyelid malpositions in Graves' ophthalmopathy. In: Gorin CA, et al, eds. *The eye and orbit in thyroid disease*. New York: Raven, 1984: 263-99.
- 9 Thaller VT, Kaden K, Lane CM, et al. Thyroid lid surgery. *Eye* 1987; 1: 609-14.
- 10 Hylkema HA, Koornneef L. Treatment of ptosis by levator resection with adjustable sutures via the anterior approach. *Br J Ophthalmol* 1989; 73: 416-8.
- 11 Henderson JW. Relief of eyelid retraction. *Arch Ophthalmol* 1965; 74: 205-16.
- 12 Grove AS. Upper eyelid retraction: treatment by levator marginal myotomy. *Orbit* 1982; 1: 21-31.
- 13 Schimek RA. Surgical management of ocular complications of Graves' disease. *Arch Ophthalmol* 1972; 87: 655-64.
- 14 Baylis HI, Cies WA, Kamin DF. Correction of upper eyelid retraction. *Am J Ophthalmol* 1976; 82: 790-4.
- 15 Beyer-Machule CK. Surgical treatment of thyroid-related eyelid retraction. *Int Ophthalmol Clin* 1989; 29: 232-6.
- 16 Harvey JT, Anderson RL. The aponeurotic approach to eyelid retraction. *Ophthalmology* 1981; 88: 513-24.
- 17 Putterman AM, Urist M. Surgical treatment of upper eyelid retraction. *Arch Ophthalmol* 1972; 87: 401-5.

Measurement of aqueous cells and flare in normal eyes

S M Shah, D J Spalton, S E Smith

Abstract

The Kowa laser cell flare meter has been recently introduced to quantify the assessment of aqueous cells and flare *in vivo* by measurement of light scattering from a low power He-Ne beam. Computer analysis of this scattered light can distinguish cells (expressed as cell count) from protein (expressed as photon count/ms), and *in-vitro* work with albumin solutions has shown that the photon count/ms is linearly related to protein concentration. This study of 106 normal eyes (53 subjects) assesses the accuracy and sensitivity of the instrument and the factors affecting the interpretation of its results. Using *in-vitro* solutions of human albumin we found a highly significant linear correlation ($r=1$, $p=0.0001$) between photon count and protein concentration. The results show that the instrument has a photon count/ms reproducibility of 8.26% and that there is a within-subject variability in photon count/ms (aqueous flare) of 12.2% in normal eyes. No significant difference in photon count/ms (aqueous flare) was found to exist between right and left eyes ($p>0.4$), between sexes ($p>0.5$), or between irides of different colour ($p>0.8$). There was also no statistically significant variation in photon counts/ms with time of day over the period of measurement (1000-1900 h) ($p=0.4$). There was, however, an increase in photon count/ms with age ($r=0.57$, $p<0.001$) and a decrease with pupillary dilatation at both 30 and 60 minutes after instillation of tropicamide 1% ($p<0.05$). An occasional cell was found in only 10.4% of normal eyes, and there was no significant increase in the cell counts on mydriasis ($p>0.05$). These findings indicate that the Kowa laser flare meter is an accurate and sensitive instrument with potential application in the investigation of the blood-aqueous barrier.

Breakdown of the blood aqueous barrier is manifested clinically as flare and cells in the anterior chamber of the eye. Assessment of these parameters is of fundamental clinical importance in anterior segment surgery, inflammatory ocular disease, and potentially in surgical audit. Up to now it has not been possible to quantify this response in a simple non-invasive manner.

The Kowa FC1000 laser flare cell meter is a recently introduced instrument that allows a quantitative measurement of flare and cells by a non-invasive technique which depends on scanning the anterior chamber with a He-Ne laser and measurement and analysis of the scattered light. The interpretation of clinical data with this machine requires a knowledge of the variations

found in normal eyes. We report a study of 53 normal subjects (106 eyes).

Materials and methods

INSTRUMENT

The Kowa laser flare cell meter consists of a He-Ne laser slit-lamp, a binocular microscope fitted with a photomultiplier, and a personal computer. The He-Ne beam has a power of 25 μ W and a diameter of 20 μ m. The beam is projected into the anterior chamber, and scattering of the beam within a sampling window (0.3 $\times$ 0.5 mm) is detected by the photomultiplier. Two measurement modes are used, one for protein concentration and the other for cell count. Computer analysis can distinguish between photons reflected from cells and protein, and *in-vitro* work has shown that the photon count/ms with albumin solutions is directly proportional to the concentration in solution.¹

Protein concentration measurement mode. The laser beam is scanned vertically for a length of 0.6 mm, covering the sampling window. Scattering of this beam is measured when it passes through this window. Measurements are also taken when the beam passes above and below the sampling window to assess the background signal (BG1 and BG2). The flare value in photon counts/ms is calculated by subtracting the mean of the two background counts from the signal value.

Cell count mode. The beam is scanned two dimensionally, 0.6 $\times$ 0.25 mm in the sampling window and the scanning volume corresponds to 0.075 mm³. A strong peak of scattered light is obtained when the beam strikes a floating cell, and the number of peaks is counted by the computer.

The instrument automatically converts from one mode to the other. Each mode takes 0.5 second, and thus the total measurement time is 1 second. Scans in which the difference between BG1 and BG2 exceeds 15%, indicative of a non-uniform background, are excluded, and the scan is repeated. Once the eye was aligned the anterior chamber was scanned five times. Each sequential scan was accepted provided the inconsistency between background counts was less than 15%.

CALIBRATION

To calibrate the instrument freshly prepared solutions of pure human albumin in saline (0.9% NaCl) over the concentration range 0-10 000 mg/l were placed in plastic cuvettes. These cuvettes were then scanned and an average of five consecutive measurements taken. This procedure was repeated twice at each protein concen-

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tration. A cuvette filled with 0.9% saline but with no albumin was used as a control.

SUBJECTS

Strict exclusion criteria were applied to select subjects to ensure normality. Subjects with diabetes, hypertension, renal and hepatic disease, or other significant systemic diseases were excluded, as were subjects with any past or present ocular disease. The use of any regular systemic or topical ocular medication or the recent use of anti-inflammatory drugs also excluded subjects. All subjects satisfying these criteria were then examined ophthalmologically, and only those with a visual acuity of 6/6 or better with no clinical evidence of anterior chamber activity or lens opacity were chosen for final inclusion in the study. Iris colour was classified as blue, Caucasian brown, Asian brown, and Negro brown.

The informed consent of each subject was obtained after the nature of the procedure had been explained fully.

FLARE VALUES

Reproducibility. Flare values were determined on both eyes of 17 normal subjects, and these measurements were repeated after an interval of five minutes. The variation between the first and second measurements was derived from the within-subject, within-eye, residual mean square and expressed as a coefficient of variation.

Subject variability. Flare values were determined in both eyes of 17 normal subjects, and these measurements were repeated one week later at the same time of day. The variation between the first and second measurements was then assessed in the same manner and expressed as a coefficient of variation.

Factor analysis. Flare values and cell counts were determined in 53 normal subjects (106 eyes) between 1000 and 1900 h. Differences between eyes and individual subjects were then analysed by multiple regression analysis to assess the effect of eye (R/L), sex, iris colour, time of day, and age on photon counts/ms.

Pupillary dilatation. Flare values and cell counts were determined in 10 normal subjects. The left eye of each subject was then dilated with tropicamide 1%, and the measurements were repeated at 30 minutes and 60 minutes after instillation of drops.

Results

CALIBRATION

A highly significant linear correlation ($r=1$, $p=0.0001$) was found to exist between photon count (/ms) and the protein concentration in solution over the range 0–1000 mg/dl (S1:0–10 000 mg/l) (Fig 1). Using the linear regression formula obtained ($y=1.35x+0.2$ where $y=\log$ of protein concentration (mg/l) and $x=\log$ of photon count (/ms)) it is possible to convert photon count into a protein concentration expressed in mg/l of human albumin.

REPRODUCIBILITY

There was no significant difference between the photon counts/ms (mean and SD) due to flare on the first (4.43, 1.09) and second (4.28, 1.08) measurements and the average coefficient of variation between the two measurements, expressed as a percentage was 8.26%. With the formula:

$$\text{Coefficient of reproducibility} = \frac{(|x-y|)}{(x+y)/2}$$

as used by Oshika *et al.*,² where x is the first measurement and y the second, the value becomes 9.54%.

SUBJECT VARIABILITY

There was no significant difference between the first (3.98, 0.81) and second (3.91, 0.81) measurements (mean, SD) taken one week later at the same time of day, and the average coefficient of variation between the two measurements, expressed as a percentage, was 12.2% or 13.3% by the formula adopted by Oshika *et al.*²

MULTIPLE REGRESSION ANALYSIS

The average age of the 53 normal subjects was 37.9 (SD 15.7) years range 17–81 years. There were 24 male and 29 female subjects. The average photon count/ms for the entire group ($n=106$) was 4.24 (SD 1.12), range 1.8–8.2, and the overall average measurement variation was 25.1% (SD 13.1%). With our calibration curve and the linear regression formula this mean photon count (per ms) of 4.24 corresponds to a protein concentration of 111 mg/l of human albumin. The average cell count for the entire group was 0.02 (SD 0.06), range 0–0.2, cells not being detected in 89.6% of eyes. The remaining 10.4% registered only 1 cell on one of the five scans, giving a cell count of 0.2 per person.

Multiple regression analysis revealed that there were no significant differences between eyes ($p>0.4$), between sexes ($p>0.5$), or between subjects with different coloured irides ($p>0.8$) (Table 1). There was also no statistically significant variation in photon count/ms with time of day over the period of measurement (1000–1900) ($p=0.4$). There was a positive correlation between age and photon counts/ms (correlation coefficient $r=0.57$, $p<0.001$) (Table 2, Fig 2). A one-way analysis of variance showed that there was a variation in photon counts/ms grouped by age as in Table 2 ($p=0.0001$). Unpaired t tests then showed that

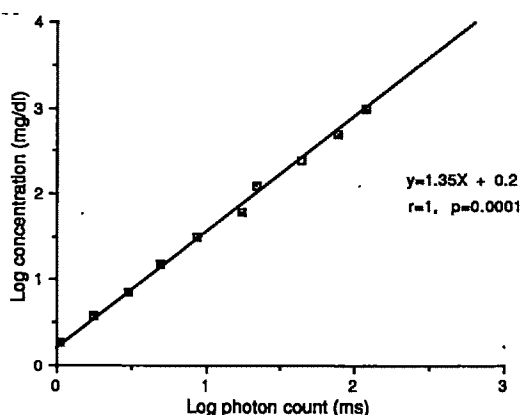


Figure 1 Photon count and protein concentration. Scatter plot of the log of protein concentration (human albumin (mg/dl)) against the log of photon count (/ms) with a superimposed line of linear regression ($y=1.35x+0.2$, $r=1$, $p=0.0001$). (SI: mg/dl=mg $\times$ 10/l.)

Table 1 Iris colour and photon count/ms

Iris	No. of eyes	Photon count/ms, mean (SD)
Blue	48	4.19 (1.32)
All brown	58	4.12 (1.05)
Caucasian brown	28	4.15 (1.25)
Asian brown	14	3.83 (0.57)
Negro brown	16	4.32 (0.98)

Table 2 Age and photon count/ms

No of subjects	Age	Photon count/ms, mean (SD)	p
24	<30	3.68 (0.59)	—
9	30–40	3.94 (0.60)	0.27
8	41–50	4.47 (0.72)	0.004*
5	51–60	5.15 (1.65)	0.0014*
5	61–70	5.25 (1.06)	0.0001*
2	>70	6.52 (1.24)	0.0001*

The p value was calculated by the unpaired two-tailed *t* test comparing mean photon count/ms of each age group with the mean value of the <30 age group.

*Statistically significant ($p < 0.05$).

the photon counts/ms were significantly higher in all age groups when compared with photon counts/ms in the <30 age group, and the level of the statistical significance was found to increase with age.

For future research studies it is important to know how small a difference could be detected between the parameters in which no difference was found. The following equation can be used to determine this:

$$n = 2 \left(\frac{\sigma}{\delta} \right)^2 (Z_{\alpha/2} + Z_{\beta})^2$$

where n = the number of subjects, σ is the standard deviation, δ is the smallest detectable difference, α is the significance level and $1 - \beta$ is the statistical power and $Z_{\alpha/2}$ and Z_{β} are the ordinates for the normal distribution.³ The factor of 2 is not required in calculations using paired data for right and left eyes.

This equation assumes that the photon counts/ms measured with this instrument in the different groups are approximately normally distributed with a range of standard deviations similar to that found in this study.

With the pooled standard deviation values in the case of unpaired data obtained in our study of 53 subjects and setting the significance level at 5%, and the statistical power at 90%, the smallest difference that could have been detected was 0.48 photon/ms for the study of right and left eyes (with $n = 53$, $\sigma = 1.069$), 1.03 photons/ms for the study on the effect of sex (with $n = 24$, $\sigma = 1.103$), and 1.02 photons/ms for the study on the effect of iris colour (with $n = 24$, $\sigma = 1.094$).

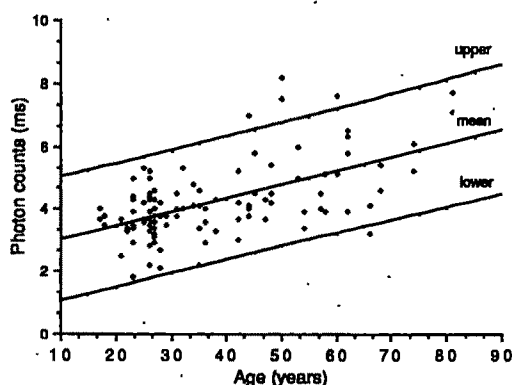


Figure 2 Photon count/ms and age. Scatter plot of photon count/ms ($n = 106$) versus age, with a superimposed line plot of the calculated mean, and upper and lower 95% confidence limits.

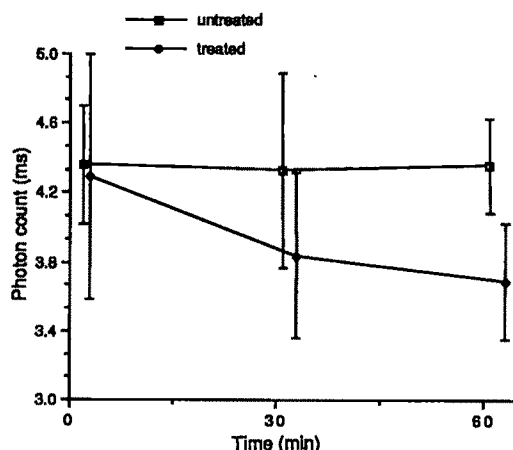


Figure 3 Photon count/ms and pupillary dilatation. Mean photon counts/ms (bars = 1 SD) in both the treated and untreated eyes of 10 normal subjects, prior to and at 30 and 60 minutes after instillation of tropicamide 1% into the treated eye. The decrease in photon counts/ms in the treated eye is statistically significant at both 30 minutes ($p = 0.03$) and 60 minutes ($p = 0.01$) after instillation of tropicamide 1%. The ratio of photon counts/ms between the untreated and treated eye at 0 minutes was 0.98 (SD 0.12) and at 60 minutes was 0.85 (SD 0.09), this decrease being statistically significant ($p = 0.0005$).

PUPILLARY DILATATION

The results are presented in Figure 3 and Table 3. A one-way analysis of variance of photon counts/ms in the treated eye grouped by time of measurement (0, 30, 60 minutes) showed a significant variation between the groups ($p = 0.04$). A similar test on the untreated eye showed no such difference ($p = 0.98$). The data were then further analysed by a paired two-tailed *t* test. There was no significant difference between photon counts/ms for the right and left eyes prior to dilatation. Photon counts/ms decreased significantly in the eye with the dilated pupil at 30 minutes ($p = 0.03$) and 60 minutes ($p = 0.01$), with no significant change in photon counts/ms in the untreated eye. The difference between the photon counts/ms in right and left eye at 30 and 60 minutes was also statistically significant ($p = 0.01$ and $p = 0.0005$ respectively).

The mean (with SD) photon count/ms for the treated eye at 60 minutes was 3.65 (0.34) and for the untreated eye was 4.32 (0.27). The ratio of counts in the treated/untreated eye was 0.847 (0.097) compared with 0.982 (0.12) prior to dilatation. This change in ratio was highly significant ($p = 0.002$).

In the untreated eye the mean background count, $(BG1 + BG2)/2$, prior to treatment was 19.35 (7.5) photon counts/ms. This increased by a mean of 0.69 photon count/ms to 20.04 (7.6) photon counts/ms at 60 minutes ($p = 0.38$). Over the same time period the signal in the untreated eye also rose by a similar amount (0.67 photon count/ms) from 23.69 (7.4) photons/ms at

Table 3 Pupillary dilatation and cell count

Time (min)	Cell count: mean (SD)	
	Untreated	Treated
0	0	0.02 (0.06)
30	0.02 (0.06)	0.06 (0.19)
60	0.04 (0.08)	0.14 (0.38)

0 minutes to 24.36 (7.4) photons/ms at 60 minutes ($p=0.44$). There was no statistically significant difference between the change in mean background count and the change in signal over the 60-minute period ($p=0.83$). In the treated eye the mean background count prior to treatment was 18.0 (7.6) photon counts/ms, and this fell by a mean 0.60 photon count/ms to 17.4 (7.5) photons/ms at 60 minutes ($p=0.14$). Over the same time period the mean signal fell by 0.11 photon/ms ($p=0.06$). This decrease in the signal was statistically significantly greater than the fall in mean background count ($p=0.03$).

There was no significant difference in the cell count between the right and left eye prior to dilatation. However, the mean cell count recorded in the dilated left eye was greater than in the untreated right eye at both 30 and 60 minutes after instillation of the mydriatic. This increase did not reach statistical significance ($p>0.05$). In the majority of subjects (8/10) no cells were detected either before or after dilatation. However, in one Asian subject with a brown iris the cell count increased from 0.2 (0.4) before dilatation to 1.2 (0.8) at 60 minutes.

Discussion

The Kowa laser flare cell meter is a sophisticated instrument that can quantify protein concentration and cells in the anterior chamber and has great clinical potential. In the assessment of any new instrument an estimate of its reproducibility and reliability is essential before further data analysis can be performed.

Using our calibration curve and the linear regression formula obtained, we found the mean anterior chamber protein concentration to be 111 mg/l. Sawa *et al.*¹ in their study of the laser flare cell meter and using bovine serum albumin found a mean concentration of 270 mg/l and Yoshimoto *et al.*² also using bovine serum albumin found a concentration of 157–186 mg/l. All these values are consistent with previous laboratory findings with aqueous samples obtained by paracentesis.³ The discrepancy between our results and those of Sawa *et al.*¹ and Yoshimoto *et al.*² may be explained by the different type and purity of albumin used in their studies.

In our study the coefficient of variation of protein-related photon/ms counts repeated after an interval of 5 minutes was 8.26%. Oshika *et al.*⁷ using a similar experimental method found a coefficient of reproducibility of 12.5%. Our results, when calculated in an identical manner to that of Oshika *et al.*,⁷ give a value of 9.54%, which compares favourably with the reported reproducibility of anterior segment fluorophotometry.⁶ These data, together with the calculation of the smallest difference between two groups detectable by the instrument, would indicate that the Kowa FC1000 is sufficiently accurate and reliable to allow an analysis of the effect of various factors on photon count/ms values derived from aqueous protein concentrations.

Oshika *et al.*⁷ have shown a diurnal variation in aqueous flare over a 24-hour period with a peak at 0600 and a trough at 1800. They found that there was a statistically significant increase in

photon counts/ms at 0200, 0600, and 1000 when compared with the value at 1800 the previous day. Further analysis of their data between 1000 and 1800 on the same day would be of interest. Although there was a decrease of 0.51 photon count/ms over this period, it is not possible from their data to ascertain whether this change is in fact statistically significant over the same working day.

In our study all measurements were performed between 1000 and 1900. Multiple regression analysis of all variables, including time of day, demonstrated that there was no significant variation in photon counts/ms during this 9-hour period. This finding may be due to the small sample size but could be of great practical importance, as it implies that the circadian effect during the working day on measurements in normal eyes is small, and measurements do not necessarily have to be performed at the same time of the working day.

Oshika *et al.*⁷ also found that there was no significant difference between measurements performed at the same time of day at an interval of 24 hours. In our study we assessed subject variability at an interval of one week, with measurements being performed at the same time of day. There was no significant difference between these two measurements, and the average coefficient of variation between these measurements was 12.2%. After allowing for the coefficient of reproducibility and diurnal variation this would indicate that there is little subject variability in photon counts/ms and hence aqueous protein concentration over this period of time.

In our study we found no significant difference in photon counts/ms between right and left eyes. A similar finding was reported by Sawa *et al.*¹ In-vitro measurements on aspirated aqueous humour have previously shown a difference in protein concentrations between right and left eyes,⁷ but our study would indicate that any such difference does not have any significant effect on the photon count/ms.

We have found a significant correlation between age and photon counts/ms. Sawa *et al.*¹ compared photon counts/ms in a group of young adults and elderly patients with early cataract and found significantly higher counts in the elderly age groups. Oshika *et al.*⁷ have found a similar increase in photon counts/ms with age. Several factors may explain this increase in photon counts/ms. It may represent a true increase in the total protein concentration in the aqueous, or a change in aqueous composition. Fluorophotometry has demonstrated a breakdown of the blood-aqueous barrier with age,⁶ and in-vitro electrophoretic studies have shown an increase in total protein concentration⁹ and also immunoglobulin concentrations with age.⁵ Inada *et al.*¹⁰ using crossed immunoelectrophoresis of aqueous humour, have also found an increase in the concentration of prealbumin, albumin, α -1 acid glycoprotein, and transferrin with age.

Another factor contributing to an increase in photon counts/ms with age may be light scatter from within the lens or reflection from the lens surface, which would be expected to be greater in cataractous eyes. In our study this is unlikely, as

subjects of all ages with visual acuities of 6/6 or better and clinically clear lenses were chosen. Despite this we still found significantly higher photon counts/ms in all age groups above 40 compared with values in the under 30 age group.

Sawa *et al*⁷ investigated the effect of pupillary dilatation and found that the photon count/ms decreased with dilatation and obtained a ratio of 0.91 (SD 0.25) between the dilated and undilated eyes of 31 normal adults, which was not statistically significant. However, Oshika and Kato¹¹ in a more comprehensive study of eyes found a significant decrease in photon counts/ms at 3 h following instillation of 5% phenylephrine and by 1 h following instillation of both 0.5% phenylephrine – tropicamide 0.5% and tropicamide 0.4% alone. They attributed this change to a pharmacological effect of the mydriatic.

In our study we found a ratio of 0.89 (SD 0.10) at 30 minutes after instillation of tropicamide and a ratio of 0.85 (SD 0.09) at 60 minutes, the latter representing a statistically significant change from the predilatation ratio of 0.98 (SD 0.12) ($p=0.002$). Whether this decrease in photon count/ms represents either a true change in aqueous composition or an artefactual change due to a change in background scatter from a dilated pupil is unknown, but dilatation does present a more homogeneous background to the measurement site, and thus minimises the effect of light scattering by surrounding ocular tissues such as the iris. Our analysis of mean background counts suggests that, although there is a reduction in background light scatter, with mydriasis this does not completely explain the decrease in photon counts/ms observed. Other possible explanations for a true change in the aqueous protein concentration or composition could be either a pharmacologically induced change in

aqueous flow rate or a change in the permeability of blood vessels in the anterior uvea. Although there have been studies on the effect of phenylephrine on these parameters,^{12,13} we are not aware of any comparable studies on tropicamide with human eyes.

In conclusion, our results indicate that the Kowa FC1000 is an accurate and sensitive instrument with potential applications in the clinical investigation of damage to the blood-aqueous barrier.

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- 1 Sawa M, Tsurimaki Y, Tsuru H, Shimizu M. New quantitative method to determine protein concentration and cell number in aqueous in vivo. *Jpn J Ophthalmol* 1988; 32: 132–42.
- 2 Oshika T, Araie M, Masuda K. Diurnal variation of aqueous flare in normal human eyes measured with laser flare cell meter. *Jpn J Ophthalmol* 1988; 32: 143–50.
- 3 Everitt BS. *Statistical models for medical investigations*. Oxford: Oxford University Press, 1989.
- 4 Yoshimoto T, Wong AS, Daher E, Sears ML. Aqueous flare measurement with laser flare-cell meter. *Jpn J Ophthalmol* 1990; 34: 57–62.
- 5 Zirm M. Proteins in aqueous humor. *Adv Ophthalmol* 1980; 40: 100–72.
- 6 Fearnley I, Spalton DJ, Smith SE. Anterior segment fluorophotometry in acute anterior uveitis. *Arch Ophthalmol* 1987; 105: 1550–5.
- 7 Kronfeld PC. The protein content of the aqueous humor in man. *Am J Ophthalmol* 1941; 24: 1121–31.
- 8 Oshika T, Kato S, Sawa M, Masuda K. Aqueous flare intensity and age. *Jpn J Ophthalmol* 1989; 33: 237–42.
- 9 Krause U, Raunio V. The protein of the pathologic human aqueous humor. *Ophthalmologica* 1970; 16: 280–7.
- 10 Inada K, Murata T, Baba H, Murata Y, Ozaki M. Increase of aqueous humor proteins with ageing. *Jpn J Ophthalmol* 1988; 32: 126–31.
- 11 Oshika T, Kato S. Changes in aqueous flare and cells after mydriasis. *Jpn J Ophthalmol* 1989; 33: 271–8.
- 12 Genderen MM, Best JA, Oosterhuis JA. The immediate effect of phenylephrine on aqueous flow in man. *Invest Ophthalmol Vis Sci* 1988; 29: 1469–73.
- 13 Araie M. Acute effects of topical phenylephrine on aqueous humor dynamics and corneal endothelial permeability in man. *Jpn J Ophthalmol* 1983; 27: 340–5.

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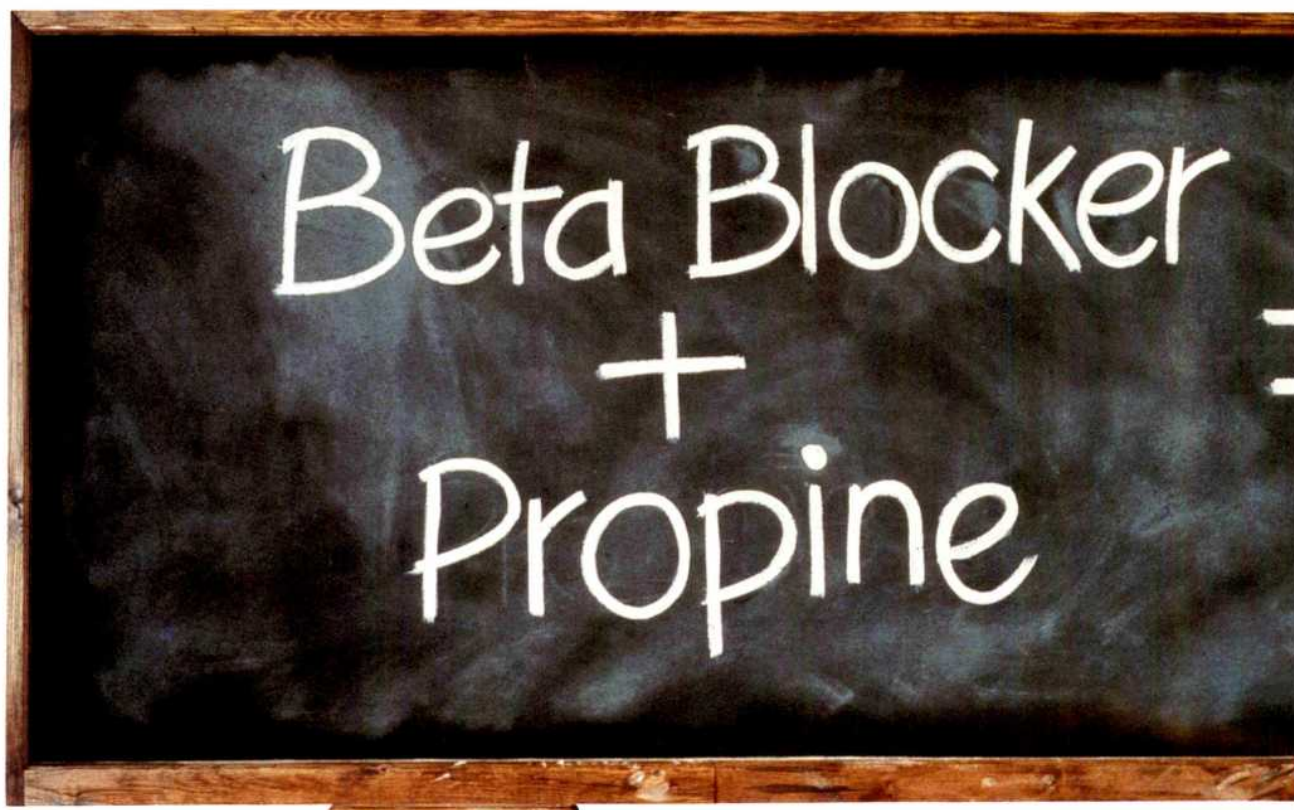
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Serological investigation of ocular toxoplasmosis

R E Holliman, P J Stevens, K T Duffy, J D Johnson

Abstract

The limitations of serological assessment in toxoplasma infection of the eye are well recognised, but the predictive value of clinical examination is not defined. We undertook a prospective investigation into the role of clinical examination and of serological findings in cases of suspected toxoplasma infection of the eye by means of the dye test and multiple IgM assays. Seventy-four cases of retinal disease and 202 control patients were studied. Patients with retinal disease had a significantly higher incidence of toxoplasma seropositivity than the control group. This was because some patients with retinal disease had acquired the infection congenitally. Half the patients investigated for toxoplasmosis were seronegative. Possible explanations for these findings included misdiagnosis, clinical uncertainty, or, the use of serology testing in the confirmation of other diseases. An excess of IgM reactivity among the retinal disease group may indicate low level immunoglobulin-M production associated with an acute exacerbation of ocular toxoplasmosis. There is a need to consider invasive procedures in cases of ocular infection and for novel techniques to aid the diagnosis of toxoplasma retinochoroiditis.

Ocular toxoplasmosis is believed to be the most common infectious disease involving the retina.¹ The great majority of cases are thought to be associated with the late sequelae of exposure in utero to the parasite.² This opinion is largely based on epidemiological evidence. It has been estimated that less than 2% of patients with toxoplasmic lymphadenopathy have retinochoroiditis related to acquired infection.³ In contrast, a prospective study of toxoplasmosis in pregnancy found that 46 of 210 (22%) congenitally infected infants suffered chorioretinitis.⁴ These figures may underestimate the problem owing to referral bias noted during the study.

Population studies have shown that the prevalence of toxoplasma infection increased with age. Consequently, if toxoplasma retinochoroiditis was associated with post-natally acquired infection, the numbers of cases should rise with increasing age. However, toxoplasma chorioretinitis is most frequent in the second and third decade of life and rare after the age of 50 years. Further evidence is provided by the lack of serological findings indicating acute infection associated with toxoplasma ocular disease and the observation that most cases show the presence of old scars at the time of diagnosis, suggesting previous activity.³

A confirmed diagnosis of ocular toxoplasmosis indicates the need for extended ophthalmic supervision, with prompt institution of short-course specific therapy during episodes of acute

exacerbation.⁵ The toxic effects of the anti-parasitic agents employed are well recognised. Consequently there is a need to establish a definite diagnosis of ocular toxoplasmosis as early as practicable.

Measurement of specific antibodies in the peripheral circulation has significant limitations when toxoplasmic retinochoroiditis is suspected. Immunoglobulin-M is rarely detected in association with ocular toxoplasmosis when standard assays are utilised. Although virtually all patients with the condition have detectable specific IgG, the relatively high prevalence of asymptomatic toxoplasmosis in the normal population markedly reduces the specificity of this finding.⁶ Ocular tissues are rarely made available for histological examination, and analysis of aqueous humour, as carried out in other countries, is undertaken infrequently in the United Kingdom.⁷ Therapeutic trials of antitoxoplasma drugs are difficult to assess, partly owing to the concurrent administration of systemic steroids.⁸ In practice the diagnosis of ocular toxoplasmosis is most often based on clinical findings, and the presence of specific antibodies in serum is used as supportive evidence to a variable extent. However, the signs of ocular toxoplasmosis are diverse,⁹ and the criteria for clinical diagnosis may vary from one ophthalmologist to another.

As a reference laboratory serving a number of specialist eye units we receive a large number of requests for the serological assessment of patients with retinal disease in whom toxoplasmosis is included in the differential diagnosis. We have therefore undertaken a prospective study to try to elucidate the relationship, if any, between clinical diagnosis and the results of laboratory tests for toxoplasma-specific antibodies.

Patients and methods

Patients were entered into the study on receipt of a serum sample with a request for toxoplasma investigation when the age and sex of the individual were stated and clinical signs of retinal disease were noted by the ophthalmologist. Only patients examined at centres known to refer samples for toxoplasma studies without prior testing or selection were included in the study. Centres practising selective referral were excluded. A control group was recruited from healthy blood donors in the same geographical region as the study group. Control samples were available only from individuals aged between 20 and 69 years. Consequently, patients with retinal disease with a recorded age beyond this range were excluded from the study.

Toxoplasma specific antibodies were measured by the dye test⁹ applied to serial dilutions beginning with neat serum. The dye test is predominantly an assay of toxoplasma-

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specific immunoglobulin-G. A sample was defined as positive when found to contain ≥ 2 IU specific antibody. Immunoglobulin-M was measured by a double sandwich enzyme-linked immunosorbent assay (DS-ELISA) and an immunosorbent agglutination assay (ISAGA).¹⁰ Statistical analysis was performed by means of the χ^2 test.

Results

A total of 111 patients with retinal disease were investigated during the course of the study. In 22 cases the age of the patient was not available, two patients were of unstated sex, seven were under 20 years old and six were aged 70 or more. These cases were excluded from further assessment. Of the remaining 74 patients comprising the study group 42 were males and 32 females, average age 36 years. The control group consisted of 202 individuals, 100 males and 102 females, average age 40 years. Toxoplasma serological findings are presented in Table 1. Of the 74 patients with retinal disease 40 (54%) had detectable toxoplasma-specific IgG compared with 45 of 202 controls (22%). Within the retinal disease group 12 patients had specific IgM detectable by ISAGA only, and one patient's serum was reactive by ISAGA and DS-ELISA. Two individuals in the control group were reactive by ISAGA alone and one by both ISAGA and DS-ELISA.

After correction for age and sex, and on the assumption of linear acquisition of antibody with increasing age, the calculated annual seroconversion rates were 1.5% and 0.6% for test and control groups respectively. The difference in seroconversion and seropositivity between the groups was statistically significant ($p < 0.001$). Although DS-ELISA reactivity was comparable in the two groups, ISAGA reactivity was significantly more frequent among the retinal disease patients ($p < 0.001$).

Discussion

Although patients referred from centres known to undertake on-site toxoplasma serological investigation were excluded from the evaluation, the study findings are susceptible to bias introduced by unrecognised primary screening. Sero-testing in a non-reference laboratory with selective referral may result in a falsely high seropositivity rate among the retinal disease group. Any study of disease prevalence based on serological investigation will be influenced by the sensitivity and specificity of the assays employed. The dye test is the accepted reference assay for the measurement of toxoplasma specific antibody.¹¹ False positive reactions are rarely produced by this test, and, when performed on neat serum, the extreme sensitivity of the assay is widely recognised. False negative dye test results have not been recorded in immunocompetent individuals.

Performance characteristics of toxoplasma specific IgM assays are less well defined, reflecting the difficulties of obtaining reference samples. However, clinical experience of the two immunoglobulin-M tests used is extensive, and a comparative evaluation of these assays has been

Table 1 Toxoplasma serological findings in patients with retinal disease and healthy individuals analysed by age and sex

Age (years)	Patient group	Sex	IgG		IgM	
			Dye test negative	Dye test positive	DS-ELISA positive	ISAGA positive
10-19	Retinal disease	M	5	5	0	2
		F	4	1	0	0
	Control	M	4	1	0	0
20-29		F	14	0	0	0
	Retinal disease	M	4	6	0	3
		F	2	4	0	0
30-39	Control	M	21	1	1	1
		F	15	4	0	0
	Retinal disease	M	4	1	0	1
40-49		F	3	4	0	2
	Control	M	14	6	0	1
		F	17	2	0	0
50-59	Retinal disease	M	3	4	0	2
		F	2	6	0	2
	Control	M	13	7	0	0
60-69		F	17	4	0	0
	Retinal disease	M	3	3	0	0
		F	1	1	0	0
Total	Control	M	13	7	0	1
		F	14	5	0	0
	Retinal disease	M	1	3	1	1
		F	2	2	0	0
	Control	M	8	5	0	0
		F	7	3	0	0
Total			34	40	1	13
			157	45	1	3

performed.¹⁰ The retinal disease and control group were found to be of comparable age and sex distribution. It is unlikely that the differences observed between the groups of patients were associated with the influence of these factors.¹²

The reasons for requesting toxoplasma investigation in the group of patients with retinal disease were varied. Serotesting may be requested when the clinical findings are characteristic of ocular toxoplasmosis. In addition, when the signs and symptoms are discordant with toxoplasma infection, serology findings may be used to exclude this diagnosis. A third category of patients will comprise individuals where the clinical findings are suggestive but not definitive, and additional information derived from laboratory investigation is needed for the final diagnosis. Other than when used to exclude toxoplasmosis, negative serological findings must indicate misinterpretation of clinical findings or 'false negative' laboratory results. Specific IgG detectable by the dye test persists for many years following exposure to the parasite, whether acquired in utero or during the postnatal period.¹¹ Given the sensitivity of dye testing of neat serum, a negative reaction is unlikely to be associated with loss of detectable antibody with the passage of time following initial exposure. In addition, negative toxoplasma serology using multiple assays has not been recorded in cases of acute or chronic infection of the immunocompetent. Consequently the finding of non-reactivity in 47% of patients with retinal disease investigated for toxoplasmosis is of interest. Insufficient details of the original clinical opinion were available to distinguish between misdiagnosis, confirmation of non-toxoplasma aetiology, or clinical uncertainty. An American study has suggested that a relative overdiagnosis of ocular toxoplasmosis occurs when based on clinical findings.¹³

Future analysis of the relation between clinical

findings and the results of laboratory tests would be greatly assisted if ophthalmologists stated their diagnosis when requesting toxoplasma investigation. The signs and symptoms of ocular toxoplasmosis are varied, and the differential diagnosis is extensive.⁸ Our findings indicate that further assessment of the predictive value of clinical examination in this condition is required. A minority of cases of retinal disease are confirmed by histological study, and the sensitivity and specificity of clinical opinion would be difficult to determine. However, the consistency and reproducibility of clinical diagnosis could be evaluated by presenting photographic slides of the retinal appearance in a number of different cases to a group of ophthalmologists and comparing the clinical interpretation of the data.

We have found significantly greater toxoplasma seropositivity among the retinal disease patients than the control group. The seropositivity and calculated seroconversion rate recorded for the control group is comparable to the findings in other regions of the United Kingdom.¹² It has been found that the duration of persistence of detectable toxoplasma specific IgM following acute infection depends on the sensitivity of the assay used and individual variation of the immune response.¹⁰ On average, specific IgM is detected in our laboratory for eight months by DS-ELISA and 18 months by ISAGA. If the IgG seroconversion rate in a series of 202 patients is 0.6%, one would expect to find one individual reactive by DS-ELISA and three having specific IgM detectable by ISAGA at the time of investigation. Consequently, the number of patients in the control group found reactive by each IgM assay is compatible with the calculated rate of IgG seroconversion.

The single blood donor found to be reactive by both ISAGA and DS-ELISA was likely to have acquired toxoplasmosis within eight months of investigation. The two control group patients who were reactive by ISAGA only were probably infected between eight and 18 months previously. These infections probably passed unrecognised, as do most cases of acute toxoplasmosis.

The calculated seroconversion rates derived from the present study are based on the assumption that acquisition of toxoplasma antibody is linear throughout the age range of the population. It is been demonstrated that there is no marked variation in the seroconversion rate between different age groups in the postnatal period.¹⁴ However, if a significant number of cases of congenital infection are included within a study population, the calculated overall seroconversion rate will exceed the actual numbers of acquired infections recorded each year. A calculated seroconversion rate is obtained by dividing the total numbers of patients with evidence of infection by the combined age of the group. Consequently a significant number of infections acquired in utero, as would be expected among a group of patients with retinal disease, will result in non-linear distribution of the seroconversions within a population.

The single patient with retinal disease found to be reactive by DS-ELISA is comparable with the

findings in the control group. However, there was an excess of serum samples from patients with retinal disease reactive by ISAGA. It has been demonstrated that the sensitivity of ISAGA is significantly greater than that of DS-ELISA for the detection of toxoplasma specific IgM, whereas both assays are highly specific.¹⁰ In consequence, ISAGA is the assay of choice for the investigation of neonatal and fetal samples.¹⁵ A possible explanation for the increased numbers of ISAGA reactions noted could be low level IgM production during an acute exacerbation of ocular toxoplasmosis.

Previous studies have not detected toxoplasma specific IgM associated with acute exacerbation of ocular disease but have used relatively insensitive methods to measure immunoglobulin-M. Our findings suggest the level of IgM production associated with an acute exacerbation of retinal disease was too low to be measured by the less sensitive DS-ELISA method but was detected by the more sensitive ISAGA technique. If confirmed, this finding would be of considerable diagnostic value, and further investigations of this aspect are required. Serial investigation of toxoplasma serology in patients with ocular toxoplasmosis during episodes of acute exacerbation of retinal disease and quiescence would be valuable.

We have demonstrated some of the limitations in the diagnosis of ocular toxoplasmosis by clinical and serological investigation. The role of aqueous humour analysis in selected cases requires consideration, and there is a need for novel diagnostic measures for cases of suspected toxoplasma infection of the eye.

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- 1 Henderly DE, Genster AJ, Smith RE, Rao NA. Changing patterns of uveitis. *Am J Ophthalmol* 1987; 103: 131-6.
- 2 Perkins ES. Hereditary and congenital factors in inflammation of the uveal tract. *Trans Ophthalmol Soc UK* 1981; 101: 304-7.
- 3 Perkins ES. Ocular toxoplasmosis. *Br J Ophthalmol* 1973; 57: 1-17.
- 4 Couvreur J, Desmonts G, Tournier G. Etude d'une série homogène de 210 cas de toxoplasmose congénitale chez des nourissons âgés de 0 à 11 mois et dépistés de façon prospective. *Ann Pediatr Paris* 1984; 31: 815-9.
- 5 Dutton GN. Recent developments in the prevention and treatment of congenital toxoplasmosis. *Int Ophthalmol* 1989; 13: 407-13.
- 6 Rothova A, van Knapen F, Baarsma GS, Kruit PJ, Loewer-Sieger DH, Kijlstra A. Serology in ocular toxoplasmosis. *Br J Ophthalmol* 1986; 70: 615-22.
- 7 Kijlstra A, Luyerdijk L, Baarsma GS, et al. Aqueous humor analysis as a diagnostic tool in toxoplasma uveitis. *Int Ophthalmol* 1989; 13: 383-6.
- 8 de Jong PT. Ocular toxoplasmosis: common and rare symptoms and signs. *Int Ophthalmol* 1989; 13: 391-7.
- 9 Sabin AB, Feldman HA. Dyes as microchemical indicators of a new immunity phenomenon affecting a protozoal parasite. *Science* 1948; 108: 660-3.
- 10 Duffy KT, Wharton PJ, Johnson JD, New L, Holliman RE. Assessment of an immunoglobulin-M immunosorbent agglutination assay (ISAGA) for the detection of toxoplasma specific IgM. *J Clin Pathol* 1989; 42: 1291-5.
- 11 Fleck DG, Kwantes W. *The laboratory diagnosis of toxoplasmosis. PHLS Monograph* 13. London: HMSO, 1980.
- 12 Dubey JP, Beattie CP. Toxoplasmosis in man (*Homo sapiens*). In: Dubey JP, Beattie CP, eds. *Toxoplasmosis of animals and man*. Florida: CRC Press, 1988: 41-60.
- 13 Swanson MW. Association of antibody titer and chorioretinal scarring in toxoplasmosis retino choroiditis. *J Am Optom Assoc* 1989; 10: 735-40.
- 14 Beverly JK, Fleck DG, Kwantes W, Ludlam GB. Age-sex distribution of various diseases with particular reference to toxoplasmic lymphadenopathy. *J Hyg (Lond)* 1976; 76: 215-28.
- 15 Holliman RE, Johnson JD. The post-natal diagnosis of congenital toxoplasmosis. *Serodig Immunother* 1989; 3: 323-7.

Yellow mercuric oxide: a treatment of choice for phthiriasis palpebrarum

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Abstract

Thirty-five patients presenting with phthiriasis palpebrarum were all treated with a regimen of 1% yellow oxide of mercury ointment four times daily for 14 days. At the conclusion of treatment there was complete resolution of the signs and symptoms of the disease. No side effects due to the treatment were reported or detected. We have shown that 1% mercuric oxide ointment is both a safe and effective treatment for phthiriasis palpebrarum. We recommend it as the treatment of choice.

Phthiriasis palpebrarum, an odd dermatophthalmological condition often encountered in children, is an infestation of the eyelashes by *Phthirus pubis* (crab lice) and its ova. The various suggested forms of treatment¹⁻¹² either have prohibitive side effects or present a technically difficult and uncomfortable form of treatment. We therefore reinstated the use of 1% mercuric oxide ointment.¹³

Subjects and methods

Thirty-five patients (16 males and 19 females) with phthiriasis palpebrarum were seen at our clinic between September 1988 and April 1989, 60% during November-December 1988. The average age was 5.4 years (range 15 months to 19 years).

Most patients (83%) were referred by their family practitioners for further management of blepharitis or conjunctivitis which had not responded to treatment with topical antibiotic drops over periods ranging from one week to three months. Four (11%) other patients were asymptomatic family members of the former group who were discovered on epidemiological examination. Another two (6%) asymptomatic patients were referred by their parents after discovering nits attached to the lashes and eyebrows.

On slit-lamp examination all the patients had typical blepharoconjunctivitis, with pubic lice and ova on their eyelashes. A louse and ova were removed from each patient for diagnostic purposes, and they were treated with 1% yellow mercuric oxide ointment applied to the lid margins four times daily for 14 days. We explained to the patients or their parents that the ointment was to be well rubbed on the lashes and eyelid margins for at least one minute in order to introduce it into the hair follicles. Since the ova hatched to release the lice approximately after one week, we decided on a two-week treatment regimen. Patients were seen weekly for two weeks and again two months after therapy was initiated. At each follow-up visit the patients

were also carefully examined for known side effects of the treatment.¹¹⁻¹⁵

A thorough epidemiological investigation was carried out, and the patients were referred to the dermatology clinic to exclude lice infestation of other body areas.

Results

By light microscopy the parasites from each patient were shown to belong to the genus *Phthirus*. At the one-week follow-up visit there was resolution of the blepharoconjunctivitis. However, some viable ova remained attached to the eyelashes. One week later all patients remained asymptomatic, with hatched ova on their eyelashes. The two-months follow-up revealed asymptomatic patients without ova on their eyelashes. No known side effects of 1% yellow mercuric oxide ointment were either reported by the patients or detected on ocular examination.

Our series included one patient who, after being asymptomatic for two months after completion of therapy, was reinfected from the original (untreated) contact. After two weeks of treatment on the same regimen he was again rendered asymptomatic.

Eleven of the 35 patients traced epidemiologically revealed the source of infestation, and efforts were made to treat them. From the patients referred to the dermatology clinic only one 18-year-old female had *Phthirus pubis* infestation in the pubic area, which was successfully treated with gamma benzene hexachloride shampoo.

Discussion

Phthiriasis palpebrarum is an uncommon condition in Israel. In view of the sharp increase in the frequency of pediculosis worldwide more cases of ocular involvement may be expected.

Pediculosis and phthiriasis occur in humans when sanitary conditions are inadequate. Typically, *Phthirus pubis* is found in the hair of the pubic and inguinal regions, the *Pediculus capitis* in scalp hair and *Pediculus corporis* on the seams of clothing. One would expect the *Pediculus capitis* to be the offending parasite and not the pubic louse, since the latter's usual site of infestation is remote from the eyelashes. However, the pubic louse is the most common cause of eyelash pediculosis. The head louse, which is frequently seen in children, is usually restricted to the scalp, and involvement of the eye region is extremely rare.¹

The pubic louse dies quickly when separated from its host, its transmission from person to person usually being by sexual contact. The

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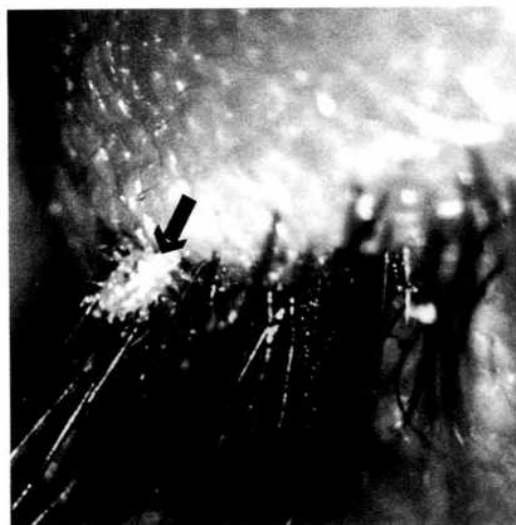


Figure 1 *Phthiriasis palpebrarum*. One adult crab louse with the stout claws gripping on to the roots of the eyelashes (arrow).

pubic area is the most frequently affected, but an infected person may transfer the organism from one hairy area to another resulting in infestation of axillary hair, beard, eyebrows, and eyelashes. Phthiriasis palpebrarum is rare in normal adults but less rare in infants who are usually infested by direct passage of the lice from the axillary or chest hair of the parents, nurse, or attendant.²

Clinical characteristics of phthiriasis palpebrarum include itching and irritation of the eyelid margins, typical of blepharoconjunctivitis. These features are by no means invariable, for lice are often found on normal palpebral margins, but frequent itching, scratching, and rubbing lead to a true inflammation, which may be intense and persistent.

The crab louse has three sets of legs attached to the anterior part of the abdomen. The middle and hind sets are wider, with a stout claw and opposing tibial thumb on each leg. Four sets of small conical feet are present on the posterior part of the abdomen. Two segmented antennae protrude from the lateral aspect of the cylindrical head. Deeply pigmented digestive material could be seen dispersed throughout the broad oval abdomen extending to the posterior aspect of the louse.

The louse may be seen gripping on to the roots of the lashes or brows with its claws (Fig 1), while the nits and empty nit shells adherent to the base of the cilia may be deposited in great numbers (Fig 2). The lice themselves may be transparent

and difficult to see, but the tell-tale nits on the lashes are readily visible.

Pediculus corporis and *Pediculus capitis* can be easily distinguished from *Phthirus pubis* by their larger size (2 to 4 mm), their flattened, elongated, triple-segmented, fused thoraces and their long slender legs. In contrast, *Phthirus pubis* is usually 2 mm or less, has a broad oval abdomen and stout claw-like legs resembling a crab's – hence its name. Crab lice are better suited for grasping the shafts of hairs and remaining more localised.^{3,4}

The effective management of phthiriasis palpebrarum requires thorough investigation and treatment of contacts, delousing of the patient, other family members, clothing, and bedding. Reinfestation can be prevented by sterilising clothing, linen, brushes, and combs at a temperature of 50°C for 30 minutes. Contaminated cosmetics should be destroyed. The epidemic spread of *Phthirus pubis* can be prevented by proper hygiene.

The most popular ocular treatment is the removal of the parasites with forceps.^{1,2} Ronchese² states: 'The infant's head is held as firmly as possible with the help of assistants. In spite of batting eyelids, screams, and tears, the struggle will be a brief one and end to everybody's satisfaction.' In co-operative patients it is possible to remove the adult parasites with forceps under the slit-lamp. However, this procedure is not without discomfort for the doctor and his young patients, and the use of general anaesthesia or sedation may be necessary.⁵

A single application of gamma benzene hexachloride with careful nit removal is usually adequate to eradicate the lice. However, disadvantages include the high potential for ocular irritation and epithelial toxicity.^{6,7} In view of reports of possible toxicity to the central nervous system this agent should be used with caution in infants, children, and pregnant women.

Anticholinesterase agents are reported to be as effective as 1% yellow mercuric oxide. But when applied in the standard concentrations used in the treatment of glaucoma unwanted ocular symptoms may be prohibitive.⁸ Another disadvantage is that they do not affect the nits themselves.

Cryotherapy has been used recently in the management of phthiriasis palpebrarum.⁹ It is advantageous in that it provides a fast cure and alleviates the need for repeated visits to the doctor. However, this treatment may be very uncomfortable and thus potentially dangerous for the young uncooperative patient. It is not generally accepted as a primary mode of treatment.

Argon laser phototherapy has the advantage of being a quick and effective method of treatment that can be done in one sitting.¹⁰ Its disadvantages include occasional but tolerable stinging and slicing of eyelash stems carrying the nits. The eyelashes regain their normal length within a few days. This method cannot be used to treat young children owing to poor patient co-operation.

Known side effects of 1% yellow oxide of mercury ointment include damage to the eyelid, conjunctiva, and Descemet's membrane, and



Figure 2 Numerous *Phthirus pubis* eggs (nits) adherent to eyelashes of the upper eyelid. Note a transparent pubic louse (arrow) attached to the lashes.

lens discolouration,¹⁵ as well as irritation and conjunctivitis.¹⁴ The patient may also complain of photophobia, blurred visual sensation, mucous discharge, itching, burning, tearing, or gritty feeling. None of the described side effects, especially those seen with long-term application of mercuric oxide ointment, were detected.¹¹⁻¹⁵

These results lead us to recommend 1% yellow mercuric oxide ointment as a cheap, simple, safe, and effective form of treatment for phthiriasis palpebrarum, especially for children.

- 1 Perlman HH, Fraga S, Medina M. Phthiriasis palpebrarum. *J Pediatr* 1956; 49: 88-90.
- 2 Ronchese F. Treatment of pediculosis ciliarum in an infant. *N Engl J Med* 1953; 249: 897-8.
- 3 Weary PE. Lice (pediculosis). In: Mandell GL, Douglas RG Jr, Bennett JE eds. *Principles and practice of infectious disease*. New York: Wiley, 1985: 1590.
- 4 Couch JM, Green WR, Hirst LW, de la Cruz ZC. Diagnosing and treating *Phthirus pubis* palpebrarum. *Surv Ophthalmol* 1982; 26: 219-25.
- 5 Goldman L. *Phthirus pubis* infestation of the scalp and cilia in young children. *Arch Dermatol* 1948; 57: 274-6.
- 6 Ben-Ezra D, Paez JH, Almeida C, Pe'er J, Zelikovitch, Bazel I. Keratoconjunctivitis following pediculocides. *Harefuah* 1983; 104: 96-8.
- 7 Reinecke RD, Kinder RSL. Corneal toxicity of the pediculicide-200 pyrinate. *Arch Ophthalmol* 1962; 68: 36-8.
- 8 Cogan DG, Grant WM. Treatment of pediculosis ciliaris with anticholinesterase agents. *Arch Ophthalmol* 1949; 41: 627-8.
- 9 Awan KJ. Cryotherapy in phthiriasis palpebrarum. *Am J Ophthalmol* 1977; 83: 906-7.
- 10 Awan KJ. Argon laser phototherapy of phthiriasis palpebrarum. *Ophthalmic Surg* 1986; 17: 813-4.
- 11 Kastl PR, Zulfigar A, Mather F. Placebo controlled double-blind evaluation of the efficacy and safety of yellow mercuric oxide in suppression of eyelid infections. *Ann Ophthalmol* 1987; 19: 376-9.
- 12 Duke-Elder S. *The ocular adnexa. System of ophthalmology*. London: Kimpton, 1974; 13: (I) 195-8.
- 13 Reynolds EFJ. *Martindale. The Extra Pharmacopoeia*. 29th ed. London: Pharmaceutical Press, 1989: 1587.
- 14 Keston BM. Conjunctivitis and blepharitis due to yellow mercuric oxide. *Arch Ophthalmol* 1931; 6: 581-2.
- 15 Abramowicz I. Deposition of mercury in the eye. *Br J Ophthalmol* 1946; 30: 696-7.



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Quality of vision through diffractive bifocal intraocular lenses

J L Jay, H S Chakrabarti, J D Morrison

Abstract

Two elderly women have each received a monofocal intraocular lens in one eye and a 3M diffractive bifocal intraocular lens in the other eye. Both eyes were shown to have equivalent retinal/neural function by measuring contrast sensitivity to laser interference fringes which bypassed refractive and other defects of the ocular media. The eyes with a bifocal intraocular lens displayed a much greater depth of focus, though at the expense of diminished contrast sensitivity compared with the normal values expected for that age. Simulation experiments suggested that the observed reduction in contrast sensitivity was not adequately explained by a simple reduction in retinal illumination of the in-focus image as might intuitively be expected from the bifocal separation of incident light to two simultaneous focal points. The simultaneous superimposition of the out-of-focus image on the in-focus image must also be considered, since this caused a significant reduction in contrast sensitivity when the retinal illumination was insufficiently above the photopic luminance threshold.

The replacement of a cataractous lens by an acrylic lens of single focal length is now very widely practised. The implanted lens restores contrast transmission over the relevant range of spatial frequencies¹ and enhances colour discrimination.² However, even in the absence of postoperative astigmatism the patient still requires a spectacle correction for either near or distance viewing, depending on the chosen power of the intraocular lens. Two zone concentric bifocal intraocular lenses are under clinical investigation, but they seem likely to depend critically on centration, and pupil size and position. To avoid this difficulty the theoretical basis for an intraocular lens with an enhanced depth of focus has been described.³ This consists of an artificial lens with a refractive power determined by the curvature of the surface, plus an additional refractive power produced by diffraction. The theory and the limitations of this type of lens have recently been reviewed.^{4,5}

The 3M Company has now introduced a diffractive bifocal intraocular lens in which an additional +2.5 DS (now increased to +3.5 DS) is conferred by a series of concentric diffraction rings ('microslopes rings') etched on the posterior surface of the lens.⁶ A survey of 55 patients who received either the +2.5 DS or +3.5 DS bifocal lens showed that some patients noted that the increased depth of focus was only at the expense of image clarity.⁷ Patients with an intraocular bifocal lens also showed a significant loss of contrast sensitivity compared with age-matched

controls with an intraocular monofocal lens at the near distance,⁸ though it must be said that both groups of patients had been selected on the basis of having 20/20 vision or better.

Recently one of us (JLJ) has had the opportunity to insert the 3M bifocal lens into one eye of two elderly women each of whom had previously received the conventional monofocal lens in the companion eye. We have set out to compare the performance of the bifocal and monofocal lenses in situ by measurement of contrast sensitivity. This involves the determination of the contrast threshold for the detection of a vertical grating pattern which has a sinusoidal variation in luminance across its horizontal extent. A schematic drawing of such a grating pattern is shown in Fig 1. Hence by repeating this test for a range of different spatial frequencies – that is, the number of cycles per degree of visual angle – a more complete assessment of visual function is obtained than is possible with the Snellen test, which gives only the point of highest acuity. It is also possible to determine how the visibility of a grating pattern of a particular spatial frequency might vary with, say, defocus, which is not possible with Snellen letters of fixed contrast. This technique was, thus, employed in our determination of depth of focus.

Patients and methods

PATIENTS

The two healthy elderly women underwent clinical assessment and surgery at the Tennent Institute of Ophthalmology. Both had previously had an extracapsular cataract extraction and insertion of a Pearce tripod monofocal posterior chamber lens of power appropriate to the corneal curvature and axial length of the patient's eye. The operation in the second eye was by extracapsular extraction followed by insertion of a 3M bifocal intraocular lens (3M Health Care, Morley Street, Loughborough LE11 1EP). The possible merits and deficiencies of this type of lens were carefully explained to each patient, who gave her consent to the operation. Both patients received the standard postoperative medication. In one patient, who had cloudiness of the posterior capsule of the monofocal eye, YAG laser capsulotomy was subsequently performed.

About three months after the second operation each patient was further examined ophthalmoscopically and was refracted for distance vision by both the Snellen test and retinoscopy. The subjective refraction for the reading distance was determined with the Faculty of Ophthalmologists' reading type. After an explanation of the experimental procedures involved, including their right to withdraw from the assessment at

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any time, each patient then gave her consent to undergo the following visual assessments, which were undertaken at the Institute of Physiology.

PRELIMINARY PROCEDURES

The optimum refraction was confirmed with the Snellen test and astigmatism fan. The diameter of the pupil of each eye was measured at intervals throughout the tests by photography.

ASSESSMENT OF RETINAL/NEURAL FUNCTION

This was undertaken to confirm that the patient has normal retinal/neural function and was not, for example, amblyopic. The contrast threshold was measured with the patient's natural pupil in response to vertical laser interference fringes of wavelength 632 nm. These were generated by focusing two collimated and converging laser beams on to the posterior nodal point of the eye, so that the interference fringes falling on the retina were essentially unaffected by the ocular media.¹ The contrast sensitivity was obtained as the reciprocal of the mean of five to eight contrast threshold readings to stationary laser interference fringes at each of spatial frequencies 10, 20, and 30 cycles/degree. These were obtained with the ascending method, by which the contrast of the interference fringes was increased by the experimenter, from a uniform field, until the interference fringes were just visible. We were concerned that one eye should not be at a disadvantage to the other owing to a difference in the effective illumination at the retina by, perhaps, different retinal sensitivities. So the intensity of the laser display was arranged to be an equal increment above photopic threshold for the left and right eyes by the following method. First, the intensity at which the uniform display was just detectable was determined by attenuation with calibrated neutral density filters after 5 minutes in darkness for each eye in turn. Then the intensity of the experimental display was arranged to be suprathreshold by the same increment for each of the left and right eyes.

ASSESSMENT OF OVERALL VISUAL PERFORMANCE

Contrast sensitivity was measured for vertical sinusoidal grating patterns generated on a Tektronix 606B monitor of screen luminance 5.3 cd/m² and peak wavelength 520 nm.⁹ Since this target was refracted by the ocular media of the eye, the contrast sensitivity measurements represent the product of ocular transmission and retinal/neural contrast sensitivity. This assessment of spatial discrimination was undertaken for spatial frequencies in the range 5–25 c/deg at a viewing distance of 2.86 m at which the display subtended 2° arc. The patient viewing with the natural pupil was refracted for this distance. In addition, the display luminance was adjusted to be an equal increment above photopic threshold for left and right eyes, as described for the laser display.

ASSESSMENT OF DEPTH OF FOCUS

Contrast sensitivity was measured for a vertical

sinusoidal grating pattern of 5 c/deg viewed at 1.0 m. At this spatial frequency the contrast threshold is relatively low, even in older subjects,¹⁰ which results in there being a substantial range of suprathreshold contrasts. On the other hand, at higher spatial frequencies the contrast threshold becomes appreciably greater, especially in the elderly, and the range of suprathreshold contrast is curtailed. This would thus limit the power of defocusing lens which could usefully be studied, since the grating pattern would not be detectable even at modest defocus. The patient was accurately refracted after both pupils had been dilated to minimise the depth of focus, which would be significantly enhanced in senile miosis and which would be different if left and right pupil diameters were unequal.¹¹ This was achieved by instilling one drop of 1% cyclopentolate hydrochloride BP (Minims) repeated after 5 minutes. In the case of M, these had only a moderate effect, and three drops of 10% phenylephrine hydrochloride BP (Minims) were subsequently instilled. A constant display luminance was employed with each eye. Contrast thresholds were measured for the left and right eyes alternately, for optimal focus and then with defocusing lenses of -2.0 DS, -4.0 DS, -6.0 DS, -8.0 DS, +1.0 DS, -1.0 DS, and -5.0 DS, in that order, in addition to a final duplicate measurement at optimal focus.

EFFECTS OF LUMINANCE ON CONTRAST SENSITIVITY

To simulate the effects of reduced intensity of the in-focus image produced by the bifocal lens, contrast sensitivity at 5 c/deg was measured for the monofocal eye at various levels of display luminance. This was done with a dilated pupil in response to logarithmic attenuations of the display luminance of -0.3 (50%), -0.6 (75%), -0.9 (87.5%), and -1.2 (93.7%), when viewing through the appropriate calibrated neutral density filter, in addition to final repeat measurements at the unattenuated luminance.

SIMULATION EXPERIMENT

Two Tektronix 606B monitors were viewed, each at 1.43 m, at which the screens subtended 4° arc, through a 38 mm cube beam splitter shown as BS in Fig 1. At this distance the smallest number of cycles (12) was well above the minimum required before contrast sensitivity was limited by the number of cycles, and the largest number of cycles (100) was below the maximum above which contrast declined owing to the characteristics of the monitor. Each screen was enclosed within a rectangular aperture in green card which matched the colour of the display. The display luminances were balanced by the addition of an appropriate neutral density filter (NDF1) in the path of oscilloscope 1. The Z modulation of each monitor was driven from the same oscillator and the timebase from the same ramp generator, so that grating patterns were of the same spatial frequency, spatial phase, and contrast and were accordingly precisely superimposable. The relationship between grating contrast and Z modulation voltage determined psychophysically¹² was similar for the two

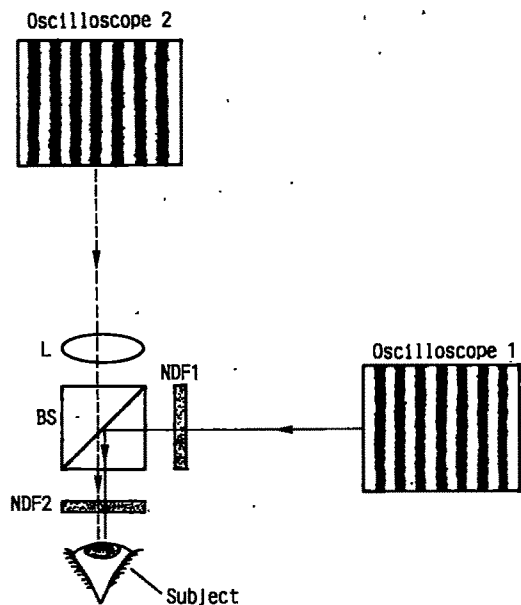


Figure 1 Apparatus for the production of two superimposed oscilloscope generated grating patterns which were viewed through the beam splitter BS. The beams were made equaluminant by the neutral density filter NDF1 (0.16 logarithmic unit), and defocus of oscilloscope 2 was effected by the trial lens L (+2.75 DS). Additional luminance decrements were produced by the neutral density filter NDF2.

monitors (namely, 0.253 and 0.265 contrast units per volt) except at relatively high voltages, where some divergence occurred: relatively few readings arose within this range and the contrast threshold was taken as the arithmetic mean of the two display contrasts. Coincidence of the two grating displays was tested by measurement of contrast sensitivity at 3, 5, 10, 15, 20, and 25 c/deg for viewing oscilloscope 1 alone and for viewing oscilloscopes 1 and 2 superimposed after the total luminance had been reduced by neutral density filter NDF2 to make it equal to oscilloscope 1 alone. These measurements proved to be identical ($p>0.25$), indicating accurate superimposition had been made. Whenever the displays had to be realigned, superimposition was always checked by this method for spatial frequencies 10 and 20 c/deg.

To simulate the condition in which the diffractive bifocal lens causes the simultaneous formation of an in-focus image and an out-of-focus image, oscilloscope 2 was defocused by a +2.75 DS trial lens positioned as near to the subject's eye as possible, which, owing to the presence of the beam splitter, was 100 mm from the estimated position of the posterior nodal point (L in Fig 1). The defocus at the posterior nodal point was

calculated to be +3.79 DS.¹³ To take account of the resultant magnification of the defocused image, oscilloscope 2 was moved further away from the beam splitter until its display outline, which though defocused was still discernible, was judged to equal that of oscilloscope 1. Further adjustments were made by viewing a square wave grating pattern of 5–6 cycles and high contrast after splitting the images so that oscilloscope 1 appeared in the upper half and oscilloscope 2 appeared in the lower half of the display. The lateral position of oscilloscope 2 was adjustable by a micrometer translation slide, the height by a scissors jack, and distance by mounting the assembly on a trolley, the movement of which was constrained by two parallel tables. The increase in magnification was compensated by moving oscilloscope 2 from 1.43 m to 1.82 m, which would have the effect of reducing the defocus caused by lens L by 0.15 DS. This gave a calculated net defocus of +3.64 DS, which is close to the diffractive power of the intraocular bifocal lens.

Contrast thresholds were first measured for 3, 5, 10, 15, 20 25 c/deg in response to the superimposed in-focus displays and, then, for the superimposed displays, but this time with that of oscilloscope 2 defocused as described above. The experiment was also repeated in the reverse order – that is, defocus followed by in-focus. But no differences were present when the experimental sequence was reversed. These measurements were undertaken for the two subjects H and D at the normal display luminance and with 0.9 logarithmic units attenuation to take account of the increased luminance thresholds of the elderly (see later). These experiments were also repeated on patient J when viewing with her monofocal eye.

To determine whether the defocused image contributed to the display contrast, contrast thresholds were measured for the superimposed displays with oscilloscope 2 defocused and with the defocused grating pattern substituted by a uniform background, which was effected by disconnecting the Z modulation of oscilloscope 2. The effects of a phase shift of the defocused image were also tested by displacement of the position of the defocused image by one half cycle, so that the defocused bright half cycle was superimposed on the in-focus dark half cycle of the in-focus grating display.

Results

The visual test data for J (age 77 yr) and M (age 71 yr) are summarised in Table 1.

Patient J had clear ocular media in both monofocal (right) and bifocal (left) eyes: the best Snellen acuity after optimal refraction was 6/5 in the monofocal eye and only 6/9 in the bifocal eye. Near acuity was equal in each eye at N5, though the monofocal eye required an additional +2.5 DS compared with only +1.0 DS in the bifocal eye. This patient told an impartial interviewer that she was delighted with the result of the second (bifocal) operation, which had restored her binocular vision. Hitherto she had experienced a lack of confidence in going out of doors and, for instance, avoided escalators. She

Table 1 Summary of visual test data

	Patient J		Patient M	
	Monofocal	Bifocal	Monofocal	Bifocal
Snellen acuity uncorrected	6/5	6/36	6/12 (–2)	6/12
Snellen acuity corrected	6/5	6/9	6/12*	6/9
Correction	nil	–0.25 DS –3.00 DC/30°	+0.75 DS +1.00 DC/120°	+1.25 DC/160°
Near acuity uncorrected	N.12	N.6	N.24 not resolved	N.6
Near acuity corrected	N.5	N.5	N.5	N.5
Correction	+2.5 DS	+1.0 DS	+3.5 DS	+1.0 DS
Natural pupil diameter	3.3 mm	4.5 mm	3.5 mm	3.5 mm
Dilated pupil	6.8 mm	6.1 mm	6.5 mm	6.0 mm

*6/9 after capsulotomy.

felt that distance vision, as judged by reading the number and destination board of oncoming buses while wearing the prescribed spectacles, was better with the monofocal eye than the bifocal eye. She could read text well with each eye, though the resolution of the telephone directory was better with the monofocal eye, again while wearing the prescribed spectacles.

Patient M also had clear media in the bifocal (right) eye, though the monofocal (left) eye showed some haziness of the posterior capsule. Hence, the best Snellen acuity after optimal refraction was better in the bifocal eye at 6/9 than in the monofocal eye at 6/12. After capsulotomy the Snellen acuity in the monofocal eye had improved to 6/9. Near acuity was N5 with each eye. The monofocal eye required an additional +3.5 DS, while the bifocal eye required only +1.0 DS. This patient was again delighted with the result of her second (bifocal) operation, for she had been bumping into furniture prior to the operation. With her spectacles she could read price tickets in shop windows equally well with

either eye and was not aware of any difference in distance vision between the two eyes. She could read well unaided with her bifocal eye, though she required additional refraction in her monofocal eye. Otherwise there was again no apparent difference in performance between the two eyes. She wholeheartedly recommended the bifocal implant.

Neither patient reported the presence of blurring or shadows at the reading distance, as had been noted previously by some patients.⁷

ASSESSMENT OF RETINAL/NEURAL FUNCTION (LASER INTERFEROMETER)

In these experiments the display luminance was arranged to be an equal increment above photopic threshold in left and right eyes to take account of any intereye difference, and viewing was with the natural pupil. The magnitude of neutral density filter required to attain threshold was slightly different for the monofocal and bifocal eyes (3.31 and 3.15 logarithmic units, respectively, for J; and 2.71 and 2.63 logarithmic units, respectively, for M). A correction was applied in the case of J but not M. The contrast sensitivities to the laser display were marginally higher in the bifocal eye at 20 and 30 c/deg than in the monofocal eye of J (Fig 2A), while it was higher in the bifocal eye at 10, 20, and 30 c/deg in M (Fig 2B). All the measured values were within the expected normal range obtained from previous data.¹ Thus the neural performance of the four eyes was judged equivalent.

ASSESSMENT OF OVERALL VISUAL FUNCTION (OSCILLOSCOPE DISPLAY)

Minor differences in photopic thresholds were again present between monofocal and bifocal eyes (3.00 and 2.70 logarithmic units, respectively, for J; and 2.63 and 2.49 logarithmic units, respectively, for M) and were compensated with the appropriate neutral density filter.

The contrast sensitivity measurements of J and M were compared with the expected normal range obtained from previous data.¹ Only those values for the monofocal eye of J fell within the normal range (Fig 2C). The contrast sensitivities for the bifocal eye of J, which were reduced by some 0.70 logarithmic unit at 10 and 15 c/deg compared with the monofocal eye, fell below the normal range. In M the contrast sensitivities, which were measured over 5–15 c/deg owing to her diminished resolution, were abnormally low for both monofocal and bifocal eyes. Comparisons between the two eyes showed no significant differences at the three spatial frequencies ($p > 0.062$). Following capsulotomy of the monofocal eye contrast sensitivity was found to be reduced slightly at 5 c/deg ($p = 0.017$) and unchanged at 10 and 15 c/deg ($p > 0.25$) (Fig 2D).

ASSESSMENT OF DEPTH OF FOCUS

Viewing in these experiments was with a dilated pupil which was within the range of 6.0–6.8 mm, when the depth of focus is negligible,¹² and for a constant display luminance for each eye. The contrast sensitivity at 5 c/deg for the monofocal

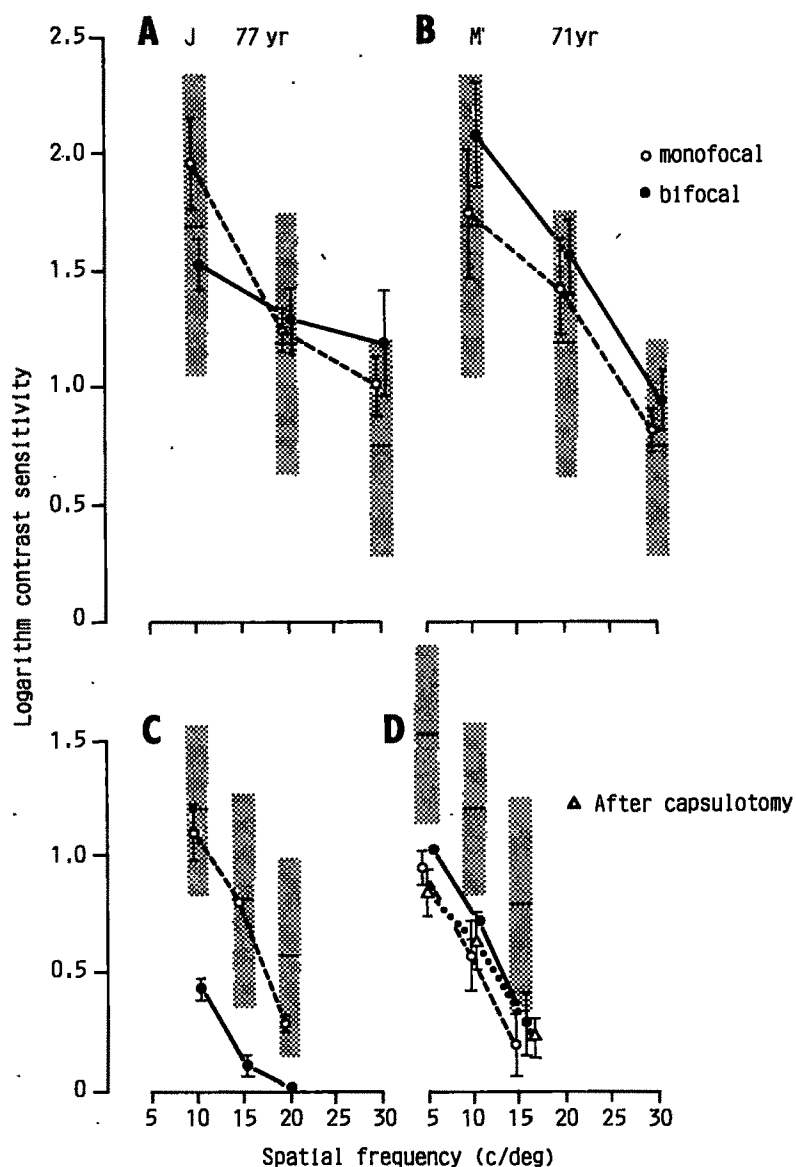


Figure 2 Contrast sensitivities to laser interference fringes (A and B) and oscilloscope-generated grating patterns (C and D) for viewing with the monofocal eye and bifocal eye. D also shows the results after capsulotomy. Note the different spatial frequency ranges in C and D. Each point is the mean with SD for 5–8 measurements. The stippled areas show the mean with 2 SD for 12 normal subjects ages 69–80 years obtained from Morrison and McGrath.¹

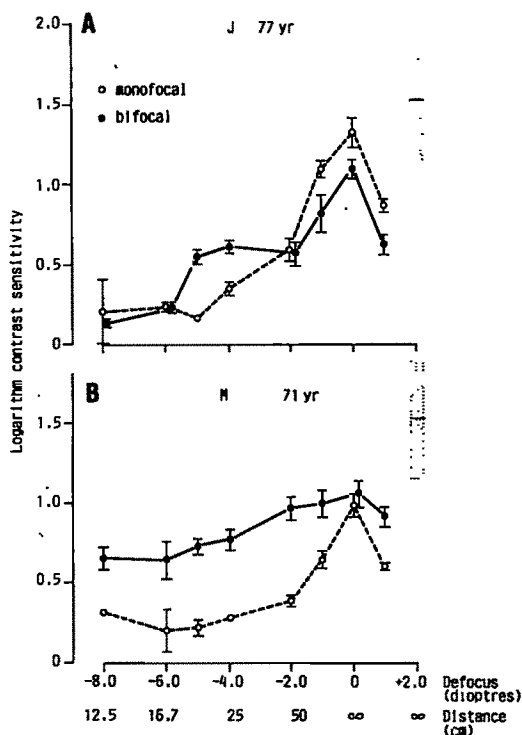


Figure 3 Contrast sensitivity at 5 c/deg for the monofocal eye and bifocal eye of the two patients (A and B) in response to viewing through trial lenses which simulated different viewing distances. Each point is the mean with SD for 5–8 measurements. The stippled zone shows the mean with 2 SD for 11 normal subjects ages 69–78 years obtained from McGrath and Morrison.¹⁰

eye of J fell within the expected normal range obtained from previous data,¹⁰ while that of the monofocal eye of M and the two bifocal eyes fell below the normal range (Fig 3A, B). With increasing defocus the contrast sensitivity for both monofocal eyes declined, with a 0.30 logarithmic unit reduction occurring at ± 1.0 DS.

The contrast sensitivities for the two bifocal eyes, however, were not affected as much by defocus. In J it was greater by 0.26 and 0.38 logarithmic units than for the monofocal eye at -4.0 DS and -5.0 DS, respectively, despite the fact that at optimum focus it was actually 0.23 logarithmic unit less than that of the monofocal eye (Fig 3A). At none of the defoci did the contrast sensitivity lie within the expected normal range. This was also the case with M, though the

reduction of contrast sensitivity for the bifocal eye with defocus was much less than with the monofocal eye (Fig 3B). At -5.0 DS the contrast sensitivity had fallen by 0.80 logarithmic unit for the monofocal eye and by 0.32 logarithmic unit for the bifocal eye. Thus in both patients the bifocal lens had conferred a considerable depth of focus which was not present with the monofocal lens.

EFFECTS OF LUMINANCE ON CONTRAST SENSITIVITY

On the assumption that the incident light is divided equally between the two focal points of the bifocal lens we tested the possibility that it was the reduction in retinal illumination as such of the in-focus image which caused the abnormally low contrast sensitivity at 5 c/deg. Contrast sensitivity was measured in the monofocal eye at 5 c/deg for progressive 0.3 logarithmic unit (50%) attenuations in display luminance. It declined monotonically with increasing attenuation in both patients (Fig 4). An attenuation in luminance of 50% resulted in a significant reduction in contrast sensitivity of 0.14 logarithmic unit in J ($p=0.0001$, Fig 4A). While this would account in part for the 0.23 logarithmic unit difference between monofocal and bifocal eyes at 5 c/deg (Fig 3A), it would not be relevant to the difference present in Fig 2C. In M the reduction was only 0.07 logarithmic unit ($p=0.22$, Fig 4B), which, when taken into account, is insufficient to explain the abnormally low contrast sensitivity in comparison with the expected normal range (Fig 3B). In young subjects the 0.3 logarithmic unit attenuation did not result in reduced contrast sensitivity, which is consistent with previous results.¹

SUPERIMPOSITION OF A DEFOCUSED IMAGE

At the normal display luminance, which was 3.53 logarithmic units above photopic threshold for subjects H and D, contrast sensitivities over the range 3–25 c/deg for the presence of the superimposed defocused display were indistinguishable from those for when the two displays were in-focus ($p>0.25$, paired t test) (Fig 5A). The mean photopic luminance threshold for the bifocal eyes of J and M was, however, 2.60 logarithmic units. So, when the experiment was repeated with an additional attenuation of 0.9 logarithmic unit, a consistent fall in contrast sensitivity over 3–25 c/deg was recorded (Fig 5B). The reduction of 0.14 and 0.28 logarithmic unit (28% and 40%, respectively) for H and D, respectively, was statistically significant ($p<0.01$). For an attenuation of 0.6 logarithmic unit contrast sensitivity was not reduced ($0.05<p<0.01$).

The contribution of the defocused image to the display contrast was assessed by substitution of a uniform background in place of the defocused display. This resulted in a further loss of 0.12 logarithmic unit (24%) ($p<0.05$) (Fig 5C, open triangles). A similar reduction in contrast sensitivity also occurred when the defocused grating pattern was displaced laterally by one half cycle (Figure 5C, inverted solid triangles). The main reduction occurred at spatial fre-

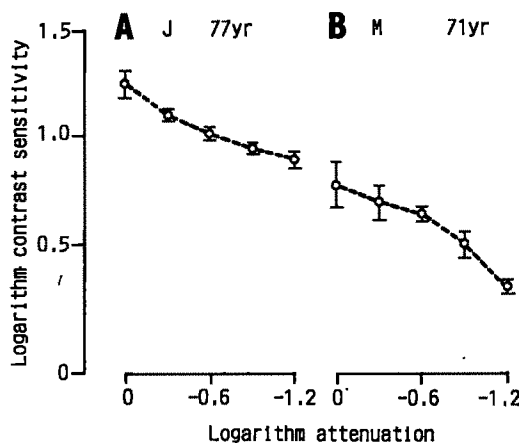


Figure 4 Contrast sensitivities at 5 c/deg for attenuation of the display luminance when viewing with the monofocal eye of the two patients (A and B). Each point is the mean with SD for 5–6 measurements.

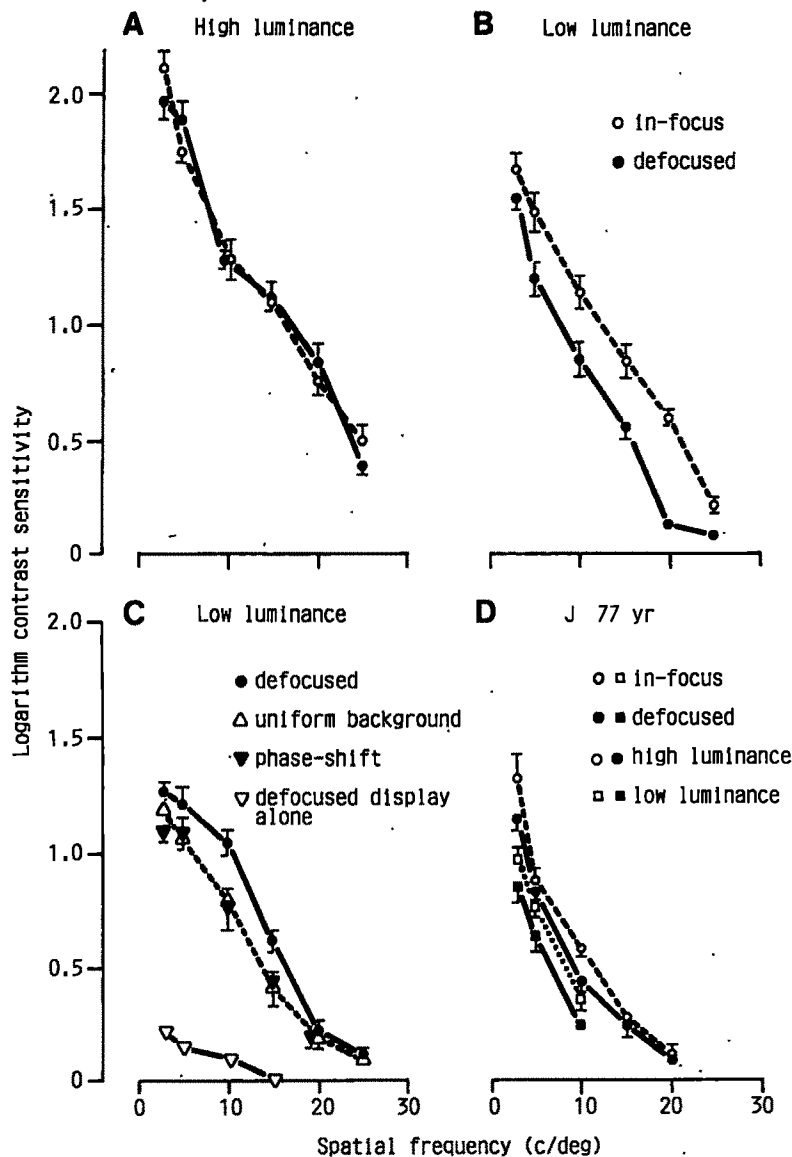


Figure 5 Effects of a superimposed defocused image on contrast sensitivity in a young subject at normal luminance (A) and at 0.9 logarithmic unit attenuation (B). Open circles denote the superimposed in-focus displays and solid symbols denote the superimposition of the defocused display of oscilloscope 2 on the in-focus display of oscilloscope 1. Substitution of the defocused display (solid circles) by a uniform background of the same overall luminance (open triangles) and by the counterphased defocused grating pattern (inverted solid triangles) are shown in C. Contrast sensitivities to the equiluminant defocused display alone are shown by inverted open triangles. In D the contrast sensitivities of patient J viewing with her monofocal eye are shown for the superimposed in-focus display (open circles and squares) and superimposed defocused display (solid circles and squares). These were measured for the normal display luminance (circles) and at 0.6 logarithmic unit attenuation (squares). J wore an additional +0.75 DS for optimal focus at the normal viewing distance of 1.43 m. Each point is the mean with SD for 5–6 measurements.

quencies of below 20 c/deg, which was interpreted as meaning that at 20 and 25 c/deg the display was defocused to such an extent that neither the in-phase nor out-of-phase grating patterns contributed to the detection of the in-focus display. This is consistent with the markedly depressed contrast sensitivities, especially those at higher spatial frequencies, which were off-scale, in response to the defocused display alone of the appropriate luminance (Fig 5C, inverted open triangles).

In the experiments with J viewing with her monofocal eye the normal display luminance, which was the same as that employed in Fig 2C, in which the monofocal eye showed a markedly superior performance to the bifocal eye was initially employed. This was 3.00 logarithmic units above the photopic threshold. In the

presence of the superimposed defocused display, contrast sensitivity was reduced somewhat compared to when the two superimposed displays were in-focus (Fig 5D, open and solid circles). The reduction of 0.09 logarithmic unit (19%) was on the borderline of statistical significance ($0.05 < p < 0.1$). When the overall luminance was reduced by 0.6 logarithmic unit, by which the monofocal eye was placed on a par with the bifocal eyes in terms of effective retinal illumination, a slightly larger reduction of 0.12 logarithmic unit (24%) which was statistically significant ($p < 0.01$) was recorded (Fig 5D, open and solid squares). This was, however, still insufficient to account for the large decrement between bifocal and monofocal eyes shown in Fig 2C.

Discussion

In our two patients the diffractive bifocal intra-ocular lens's main purpose in conferring an additional depth of focus than with the monofocal lens was shown to have been fulfilled. However, this appeared to be at the expense of spatial resolution, which was markedly impaired. In terms of contrast sensitivity, in one patient, the performance of the bifocal lens in situ was on par with the monofocal eye, the performance of which was suspected to be suboptimal. In the other patient the bifocal eye was markedly inferior to the monofocal eye.

RETINAL/NEURAL FUNCTION

The retinal/neural contrast sensitivities of all four eyes fell within the expected normal range and indeed were broadly similar. This suggests that there was no adverse effect of the operation on retinal/neural function. Moreover, there did not appear to be a deleterious effect of the diffraction rings of the bifocal lens on the contrast of the laser interference fringes. This may be surmised to be due to the fact that the two laser beams incident to the eye are focused by the Maxwellian lens on to the posterior nodal point of the eye. Thus the beam diameter at the bifocal lens is relatively small in comparison with the spacing of the diffraction rings, the first of which may be expected to have a diameter of 1.07 mm for +3.5 DS.⁴ In the case when a large collimated beam is incident to the diffraction rings, a circular diffraction pattern would be generated for each beam, and these themselves would mutually interfere. No such patterns were ever reported, and only the vertical interference fringe pattern was ever detected by the patients, even at high contrasts. Thus it becomes feasible to assess the deficit caused by the bifocal lens on the resolution of the oscilloscope-generated grating pattern by an estimation of the Snellen acuity expected from the laser interference fringe contrast sensitivities. On the basis of the data in Figure 2A and B a Snellen acuity of 6/6 or 6/5 would reasonably have been expected for the bifocal eyes instead of the recorded 6/9.¹

OVERALL VISUAL FUNCTION

It would appear that a penalty has been paid in

our two patients in terms of best distance acuity in order to gain depth of focus. This is most apparent in patient J, to whom the difference was readily discernible. In M the monofocal and bifocal eyes did show a similar level of performance, though in this patient we believe that this was attributable to the anomalous underperformance of the monofocal eye. In this respect it was noted that capsulotomy of the monofocal eye with the hazy posterior capsule did not result in improved vision (Fig 2D), which indicates that the capsule was unimportant in causing this anomaly. Other such anomalies have been encountered occasionally in a previous study.¹ No definite explanation can be given other than to remark that irregularities of the cornea and pathology of the retina might be excluded, since both would adversely affect the laser interference fringe contrast sensitivity.

The division of incident light between the two focal points by the bifocal lens, and hence, a reduction in luminance of each in-focus image, may reasonably be expected to have some effect on contrast sensitivity (Fig 4), though this would not account for the observed reduction in contrast sensitivities under the experimental condition where the effective luminance of left and right eyes had been made equal (Fig 2C, D). However, it must be said that by simply matching luminances for the monofocal and bifocal eyes the possibility of a reduced illumination of the in-focus image is not completely excluded. First, it does not follow that the two eyes should have equivalent photopic thresholds, especially in the elderly, where there may have been differential effects of aging; and, secondly, the in-focus image will have superimposed upon it the out-of-focus image. In the luminance matching procedure this would serve to cause an underestimation of the luminance of the in-focus image.

However, we believe that another explanation, other than a simple reduction in luminance, should be considered. We have demonstrated that the superimposition of the out-of-focus image on the in-focus image has a deleterious effect on contrast sensitivity when the display luminance is an insufficient amount above the photopic luminance threshold in both the control subjects and the patient J. In these experiments our estimate of an age related increase in photopic threshold of 0.9 logarithmic unit, based as it was on a limited number of eyes, is consistent with previous data.¹⁴ Patient J actually had a somewhat lower than expected luminance threshold for her monofocal eye, but, once taken into account, contrast sensitivities were significantly reduced in the presence of the superimposed defocused image. The reduction, however, was insufficient to explain the marked deficit recorded in Fig 2C, for which other explanations must be sought. It must be emphasised that the cause must be optical rather than neural, since retinal contrast sensitivities were normal (Fig 2A). One unknown factor which has yet to be evaluated theoretically⁵ is the possibility of a phase shift by the diffractive optics. This would cause a further decrement in contrast sensitivity (Fig 5C), though again not to an extent that would completely explain the deficit shown in Figure 2C.

Several further complexities exist. The performance of the bifocal lens will depend critically on the accuracy of the position of the diffraction rings, since the interval between rings must decrease with eccentricity.⁴ Thus the machining of the diffraction rings and centring of the lens would need to be precise to ensure constructive interference of the diffracted light rays; otherwise destructive interference would arise. Secondly, the characteristics of the diffractive lens are specific to a certain wavelength of light, since refraction is *directly* related to wavelength. In other words, the 41% transmission specified by the manufacturer is applicable to only one (unstated) wavelength. On the assumption that the specifications are for green light we may surmise that the performance obtained in response to our green oscilloscope display is in fact the best possible and would be poorer for other wavelengths.⁵ Hence it would appear from the lower than expected contrast sensitivities for the two bifocal eyes (Fig 2C, D) that there are factors yet to be recognised in the explanation for these deficits. This would perhaps justify the mounting of a larger scale in-depth study of patients with a monofocal implant and diffractive bifocal implant in their respective eyes. Our more detailed experimental study thus complements the clinical study of Percival⁷ and the photographic analysis of Zisser and Guyton.¹⁵

If the experiment in which a defocused image was superimposed on the in-focus image is a reasonable simulation of the effects of the diffractive bifocal lens, we could expect that no measureable impairment of visual performance would arise, provided the luminance was sufficiently high with respect to that individual's photopic threshold, irrespective of age. This disregards the possible contribution of the factors of a phase - shift, chromatic aberration and decentration, which have yet to be evaluated. However, with insufficient illumination a significant decrement in contrast sensitivity would be predicted, especially in older patients, whose luminance threshold is raised as part of the normal aging process.¹⁴ This decrement would be predicted to be exacerbated for viewing within the scotopic range. Hence under conditions of low illumination the diffractive bifocal intraocular lens may not reasonably be expected to give the same quality of vision as the monofocal lens.

Some patients may, however, happily trade diminished contrast sensitivity in distance vision for a greater depth of focus. This may apply to elderly patients who have a more sedentary life style and for whom resolution of distant objects is relatively unimportant, and to younger patients who still have accommodation in one eye and who might thus prefer the bifocal intraocular lens in the companion eye. On the other hand the monofocal implant may be the choice of those for whom distance vision is of particular importance. This choice should be considered in terms of the prospective patient's photopic luminance threshold. Plainly it is impracticable to make determinations on a cataractous eye, though regard could profitably be given to the previously well established data across the lifespan.¹⁴ Accordingly, the potential difference in performance

between the diffractive bifocal and monofocal lens should be explained fully to the patient.

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- 1 Morrison JD, McGrath C. Assessment of the optical contributions to the age-related deterioration in vision. *Q J Exp Physiol* 1985; 70: 249-69.
- 2 Jay JL, Gautam VB, Allan B. Colour perception in pseudophakia. *Br J Ophthalmol* 1982; 66: 658-62.
- 3 Freeman MH. Improvements in or relating to artificial eye lenses. *UK Patent GB 2101764B*. London: Patent Office, 1984: 1-32.
- 4 Charman WN. Diffractive bifocal contact lenses. *Contax* 1986; May: 11-7.
- 5 Klein SA, Ho Z-Y. Multizone bifocal contact lens design. *SPIE* 1986; 679: 25-35.
- 6 Simpson MJ. The diffractive multifocal intraocular lens. *Eur J Implant Ref Surg* 1989; 1: 115-21.
- 7 Percival SPB. Prospective study of the new diffractive bifocal intraocular lens. *Eye* 1989; 3: 571-5.
- 8 Olsen T, Corydon L. Contrast sensitivity in patients with a new type of multifocal intraocular lens. *J Cataract Refract Surg* 1990; 16: 42-6.
- 9 Kay CD, Morrison JD. The effects of a single intramuscular injection of atropine sulphate on visual performance in man. *Hum Toxicol* 1987; 6: 165-72.
- 10 McGrath C, Morrison JD. The effects of age on spatial frequency perception in human subjects. *Q J Exp Physiol* 1981; 66: 253-61.
- 11 Campbell FW. The depth of field of the human eye. *Optica Acta* 1958; 4: 157-64.
- 12 Campbell FW, Green DG. Optical and retinal factors affecting visual resolution. *J Physiol (Lond)* 1965; 181: 576-93.
- 13 Duke-Elder S, Abrams D. *Ophthalmic optics and refraction. System of ophthalmology*. London: Kimpton, 1970; 5: 74-6.
- 14 Weale RA. *Biography of the eye*. London: Lewis, 1982: 268.
- 15 Zisser HC, Guyton DL. Photographic simulation of image quality through bifocal intraocular lenses. *Am J Ophthalmol* 1989; 108: 324-6.

MINI REVIEW

Bifocal intraocular lenses

The paper on quality of vision through diffractive bifocal intraocular lenses by Jay, Chakrabarti, and Morrison offers a careful and detailed study which will be of value to implant-lens surgeons who are or who are considering implanting bifocal intraocular lenses (IOLs). It may well fill in the physiological data gap of some of the more subjective papers on the topic. Good science with careful inbuilt checking for error has been used to assess depth of focus and contrast sensitivity.

The paper also raises questions of relevance to all types of bifocal intraocular lenses – the ‘centre drop’ design as well as the diffractive types. Both require careful centration, though the diffraction type less so, because both distance and near diffraction rulings are present in almost all zones of the lens.¹ The latter may, however, reduce light transmission slightly because of the machined or moulded-in diffraction ruling structure, and this has been shown to cause problems of reduced near vision in dim light. It may also introduce diffraction grating spectral effects, though these do not figure prominently in the literature.¹ On the other hand the diffractive type retains a balance between luminosity of the near and distance images for all pupil sizes.² This balance can be severely disturbed for the centre drop type, even to almost total extinction of the distance image in bright light miosis. Equally decentration by 2 to 3 mm can obscure much of the central near vision zone.

One must ask the question, is the simultaneous perception of both near and distance images in the same retinal focal plane a physiological state? While a blurred image of either distance or near in one scene containing both planes may well be physiological, superimposition of both these sharp images in the focal plane may reduce contrast sensitivity by wave interference at the photoreceptors.³ Superimposition of two sharply focused near and distance images only rarely occurs physiologically by increased depth of focus at very bright luminance and with small pupil sizes.

There is also debate whether the diffractive type, with its inherently poorer optical quality and reduced resolution, can compare with the discrete bifocal ‘centre drop’ lenticle type.⁴ The latter also have disadvantages with a miotic pupil, so that distance images are inevitably out of focus through the near vision centre lenticle at bright ambient luminance due to near total iris masking of the distance vision annulus.

In spite of these constraints many implanters of bifocal IOLs comment subjectively on their happy patients’ response to these lenses,^{4,5} though one reports a 14% negative response,⁶ and another that only 50% are tolerated.⁷ The truth probably lies between these views. Some people do well with bifocal spectacles and adapt rapidly while others never do. It would be a brave surgeon who would implant a bifocal IOL in a non-tolerator of bifocal glasses. Similarly bifocal contact lenses of the annular or the lower segment type are often poorly tolerated and rarely worn in the long term. Furthermore, the Diffrox type contact lenses raise much the same debate regarding contrast sensitivity and visual transfer function.

Some doubts are now being raised by experienced implanters of bifocal lenses.⁸ Percival comments on both poor optical quality and tolerance.⁶ Kasten-Aker and Kaufmann go further and express the increased risk of error and the

possibility that the lens may have to be removed or replaced later with all its attendant surgical problems and hazards – a task few implanters approach lightly.⁷ Though endocapsular or ‘in the bag’ implants may be easier to remove, severe disturbance to the eye can occur with trapped and fibrosed haptic loops, amputated loop remnants left in the eye, and disturbance of the iris or ciliary sulcus by haptic-uvea or ciliary sulcus tunnel adhesions. Even severe disturbance or loss of vitreous with its attendant risk of cystoid macular oedema can occur.

Kasten-Aker and Kaufmann cite 10 to 20% of patients unhappy enough to insist on removal of the IOL, especially when they cannot sort out the two images.⁷ They state, ‘Thus we create a permanent problem that cannot be fixed by spectacles’, whereas monofocal IOLs almost invariably can be balanced or focused by spectacles, and the non-tolerant prescription for bifocal spectacles can easily be remedied by separate pairs of glasses.

This debate is of course incomplete and no one would wish to stifle innovation and development. The bifocal intraocular lens is undoubtedly a valuable innovation well within the ability and technique of the average implant surgeon. The future may lie with accommodating intraocular lenses, potentially a more physiological status. Some extraordinary devices are appearing.⁹ There is even the suggestion of a molecular polymer transistor lens which might change refractive index, or shape, by altering cross linkages, and all this under the influence of the small electric potentials on the nearby ciliary muscle.¹⁰ This sounds far fetched, but to some extent the future in science is arriving faster than we can anticipate, and nowhere faster than in intraocular lens surgery and technology. More probable are accommodating IOLs of very pure methacrylate polymers in the liquid glass phase inserted in super flexible envelopes in the posterior chamber or injected into the closed capsular bag itself, and there subject to zonular forces.¹¹ As Kelman has said, ‘Our aim for the turn of the century must be to return our patients’ sight after cataract surgery to that state of quality and accommodation that they had enjoyed at 28 years of age.’¹² While reduced retinal performance in age may well curtail this target, it is nevertheless a praiseworthy destination for the millenium.

G MUNTON

- Wallace RB. Multifocal intraocular lenses: demands for surgical precision. *Implants in Ophthalmology* 1989; 3: 77–8.
- Lehmann RP. Experience with diffractive multifocal IOL: follow up on a small series. *Implants in Ophthalmology* 1989; 3: 74–6.
- Olsen T, Corydon L. Contrast sensitivity as a function of focus in patients with the diffractive multifocal intraocular lenses. *J Cataract Refract Surg* 1990; 16: 703–6.
- Percival P. Early experience with the diffractive bifocal lens. *Eur J Implant Refract Surg* 1989; 1: 3–4.
- Percival P. Indications for the multizone bifocal implant. *J Cataract Refract Surg* 1990; 16: 193–7.
- Percival SPB. Multifocal IOL removal. *Ocular Surgery News* (international edition) 1990; 1: 4.
- Kasten-Aker AG, Kaufmann HE. Should multifocal IOLs be used? *Ocular Surgery News* (international edition) 1990; 1: 8–21.
- Ellingson TF. Explanation of 3M diffractive intraocular lenses. *J Cataract Refract Surg* 1990; 16: 697–703.
- Kerchner RM. One year results of the compressible disk lens. *Ocular Surgery News* (international edition) 1990; 1: 12–3.
- Marshall J. *Trends in ophthalmology*. London: St Thomas's Hospital, 1989.
- Tsutomu H, Takako H. Method, potential uses of dumbell capsulotomy. *Ocular Surgery News* (international edition) 1990; 1: 12–3.
- Kelman C. Cataract and implant surgery past, present and future. Kelman Lecture. 8th Congress European Intraocular Implants Council. Dublin: 1990.

CASE REPORTS

Pattern of arterial involvement of the head, neck, and eyes in giant cell arteritis: three case reports

Z Butt, J F Cullen, E Mutlukan

Abstract

The findings of two post-mortem examinations and one CT scan of patients with biopsy proved giant cell arteritis (GCA) are presented. The presence or absence of intracranial involvement in GCA is discussed.

Giant cell arteritis (GCA) is rarely fatal, and references to the condition in post-mortem material are uncommon.¹⁻¹⁶ However, this may be related to non-recognition of a fatal outcome in patients with GCA and because post-mortem examinations of elderly patients dying from vascular disorders are not routinely carried out. GCA may be concealed among the cases diagnosed as ischaemic catastrophes due to arteriosclerosis.¹⁷

Patients suffering from GCA have a range of symptoms including headache, jaw claudication, fever, anorexia, and loss of vision. However, atypically they may present with symptoms of cerebral ischaemia, the aetiology of which may be confused with that of other conditions such as arteriosclerosis. We suggest that such atypical symptoms may be secondary to embolism and that the diagnosis of GCA should not be overlooked. A raised erythrocyte sedimentation rate together with positive findings on temporal artery biopsy should help in confirming or refuting the diagnosis. GCA is treatable, and treatment leads to symptomatic improvement.

Case reports

CASE 1

An 80-year-old man presented in 1973 with a three-month history of temporal headaches, influenza-like symptoms, and anorexia. Acute loss of vision in the right eye had occurred two days previously and acute loss of vision in the left eye followed on the day of presentation. Visual acuity was no perception of light in the right eye and perception of light in the left eye. His pupils did not react to light, and there was bilateral oedema of the discs. The Westergren erythrocyte sedimentation rate was 90 mm/h. Anterior ischaemic optic neuropathy secondary to GCA was diagnosed, and high-dose corticosteroid treatment was initiated. His mental condition deteriorated over the next few days, and he was thought to have sustained a cerebrovascular accident. He became comatose and died secondary to hypostatic pneumonia. His temporal

arteries at necropsy showed characteristic changes of GCA (see below).

Post-mortem findings. Macroscopically the main arteries at the base of the brain were virtually free from atheroma, but a plug of rather firm clot was present in the stump of the right internal carotid. The circle of Willis was normally constituted. Several haemorrhagic infarcts were noted in the cerebrum (frontal, parietal, temporal, and occipital lobes) and cerebellum. Microscopic examination confirmed that these were very recent, practically terminal, infarcts. Occasionally small meningeal arteries overlying the cortical infarcts were noted to contain recent thrombus, but in none of the sections was there evidence of giant cell arteritis.

Sections of the temporal, ophthalmic, vertebral, internal carotid (in neck), external carotid, left common carotid, and coronary arteries showed changes typical of giant cell arteritis. Histological abnormalities noted included: (1) Diffuse fibrous thickening of the intima associated with mucinous changes and narrowing or occlusion of the lumen. (2) The presence of organising mural thrombus (both internal carotid arteries). (3) Fragmentation and disappearance of the internal elastic lamina. (4) Chronic inflammatory changes which were transmural but principally involved the media, especially in relation to damaged internal elastic lamina.

The inflammatory cell infiltrate was predominantly composed of lymphocytes and epithelioid cells along with a few plasma cells and variable numbers of Langhans giant cells. Foci of fibrinoid degeneration were seen in the deeper layers of the fibrosed intima and in the media in some sections. In many of the affected vessels severe atheroma complicated the histological picture. The terminal segment of the right internal carotid artery showed no evidence of GCA, containing only red blood clot (not thrombus).

Examination of the globes showed: (1) Oedematous optic discs but normal and patent central retinal vessels. (2) Infarction in the retrolaminar region of the optic nerve (Figs 1 and 2). (3) Chronic inflammatory changes of the adjacent posterior ciliary arteries. Many of the vessels were occluded.

CASE 2

An 86-year-old woman presented in June 1988 with an eight-day history of loss of vision in her

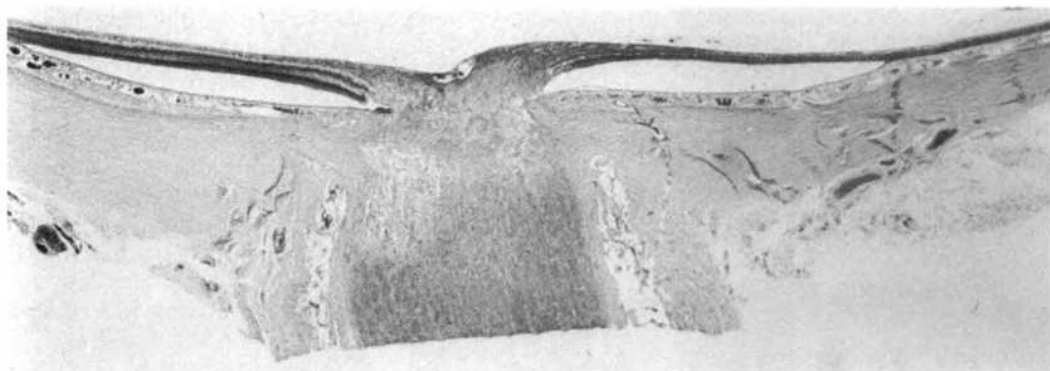


Figure 1 Histological section of right optic nerve. (H-E and eosin stain, $\times 20$.)

right eye. This was associated with decreased appetite, weakness, jaw claudication, general malaise, and shoulder stiffness.

She had had a right cataract extraction with intraocular lens implant in August 1987. She was dependent on her right eye for vision because her left eye had a dense cataract. Visual acuity was 6/60 in the right eye and perception of light in the left. The right pupil was unreactive to light, but pupil adhesions to the anterior vitreous were present. The left pupil reacted sluggishly to light. Her optic discs were pale but not swollen. She had a total bilateral ophthalmoplegia. The patient did not co-operate for visual field testing. A provisional diagnosis of posterior ischaemic optic neuropathy was made at this time.

The Westergren ESR was 110 mm/h, and high dose corticosteroid treatment was started. The diagnosis of GCA was confirmed by temporal artery biopsy. X-rays of the skull, optic foramina, and pituitary fossa were normal. Unfortunately there was further visual reduction to no perception of light in the right eye and perception of light in the left eye.

A CT scan suggested symmetrical cortical infarctions round the calcarine fissure, features

consistent with cortical blindness (Fig 3). However, this was not confirmed by post-mortem examination performed three months later (see below).

In September 1988 she had a massive gastrointestinal haemorrhage, probably a complication of high-dose steroid treatment, and died.

Post-mortem findings. Microscopically, sections of the cerebral cortex and basal ganglia showed a few tiny old infarcts. The calcarine cortices were normal. Neither the arteries on the surface of the brain and subarachnoid space nor within the brain substance showed any evidence of arteritis. The carotid bifurcations were grossly atheromatous but not particularly stenosed. One or two small arterial twigs in the surrounding connective tissue were thick walled, had probably been thrombosed, and showed sparse lymphocytic infiltration of their walls, most marked in the adventitia. No giant cells were identified in relation to the internal elastic lamina. Similar changes were present in the arterial twigs accompanying the optic nerves, including the ophthalmic artery but not the central retinal artery. A solitary microscopic infarct was present in the right optic nerve in the retrolaminar region. Thus

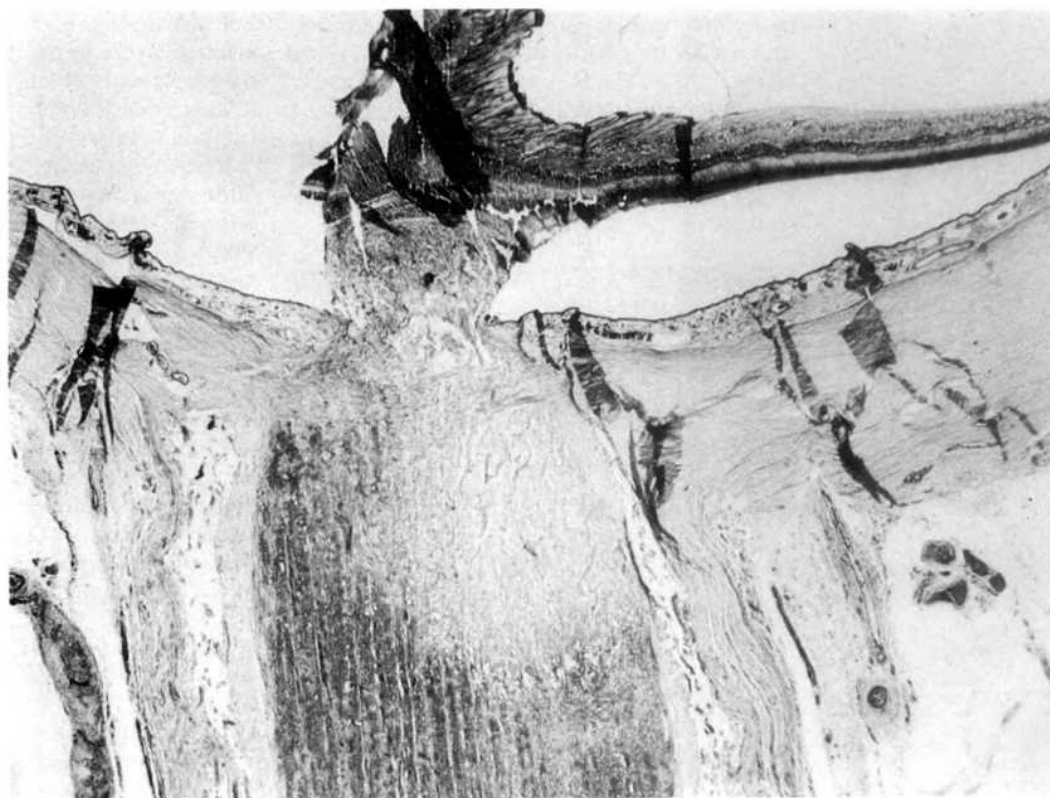


Figure 2 Histological section of left optic nerve. (H-E and myelin stain, $\times 55$.)



Figure 3 Case 2. CT scan.

these chronically inflamed scarred small arteries were considered to represent a burnt out version of GCA.

CASE 3

A 65-year-old woman presented in 1964 with a three-week history of severe frontal headache associated with temporal tenderness. There were no ocular symptoms and her vision was normal. The Westergren ESR was 83 mm/h, and biopsy of her right temporal artery showed classical changes of GCA. Corticosteroid treatment was started and led to symptomatic improvement.

Seven years later, while still on carefully monitored treatment, she presented with an episode of visual loss in the right eye, acuity falling from previously recorded 6/6, N5, to 6/60, N18. She had a right afferent pupillary defect and a swollen pale disc. The ESR was 45 mm/h. Details up to this time were reported by Cullen.¹⁸ A repeat right temporal artery biopsy showed no evidence of active arteritis. A diagnosis of right anterior ischaemic optic neuropathy was made. Her dosage of steroids was increased, but unfortunately there was no visual recovery.

It has been suggested that despite negative temporal artery biopsies¹⁸ the disease in this case remained active in the posterior ciliary arteries, and this was reflected by moderately raised ESR readings.

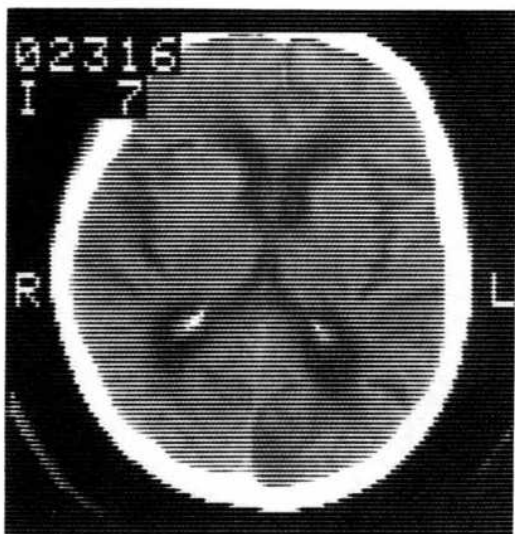


Figure 4 Case 3. CT scan.

In July 1987 she was seen again with a 10-day history of loss of vision in her left eye which had occurred on awakening. The ESR was 75 mm/h. On examination her vision was perception of light in the right eye and hand movements in the left eye. The left pupil was reactive to light and the disc was normal. A CT scan showed marked widespread cortical atrophy and focal areas of low density related to the tip of the occipital pole on both sides, left more than right, which were consistent with bilateral occipital infarction (Fig 4). She died a year later. A necropsy was not performed.

Discussion

In our three patients changes typical of GCA were present in the temporal arteries, proved by temporal artery biopsy in cases 2 and 3 and by positive histological changes in the post-mortem examination of the superficial temporal and other arteries in case 1. Necropsy carried out on two patients with proved cerebrovascular disease related to GCA failed to identify intracranial GCA. The cerebral infarcts found were the results of embolism from extracranial vessels, which were damaged by arteritis and atheroma and contained thrombus, rather than from lesions of the intracerebral arteries themselves. This was confirmed by the multiple, haemorrhagic nature of the lesions.

In case 3 there was evidence of cerebral involvement on CT scan. However, it is not possible to say whether this was due to lesions of the intracranial or extracranial vessels. This case therefore neither confirms nor contradicts our initial hypothesis that cerebrovascular disease in GCA may not be due to intracranial arteritis. However, whatever the pathogenesis of this patient's condition, it must allow for the possibility of simultaneous infarction of both occipital lobes. The simplest explanation would be embolism (due to thrombus from arteritic vertebral arteries) to the bifurcation of the basilar artery, with fragments of embolus being shed more or less symmetrically between the two posterior cerebral arteries.^{7 12 14 15}

Intracranial vessel involvement is suggested (although infrequently) in a number of published articles.¹⁻⁹ However, the basis for such a conclusion is not always certain. There is clinical, post-mortem, and angiographic support for intracranial involvement, but post-mortem studies are the most reliable source of information, as angiographic and clinical evidence may be open to the criticism that coincidental arteriosclerosis or some other disease process could be the cause of cerebral involvement. Post-mortem evidence has shown involvement of the intracranial part of the internal carotid, vertebral, and basilar arteries and arteries of the base of the brain.^{1 2 5 7-9} Angiographic abnormalities have been noted consisting of either irregular areas of stenosis and dilatations¹⁰ or a saw-toothed appearance⁶ in intracranial arteries. Hinck *et al*¹⁰ found no post-mortem evidence of GCA related to the angiographic abnormalities, whereas Hirsch *et al*⁶ confirmed their angiographic findings by pathological examination, which showed features consistent with GCA in the anterior,

middle cerebral, and entire part of the basilar artery. The authors suggest that angiographic abnormalities may in fact be non-specific and related to embolic phenomena, thrombi, or atheroma, and may not always be conclusive of intracranial pathology due to GCA.¹¹ Similar cerebral angiographic findings have been reported in other types of arteritis such as polyarteritis nodosa, rheumatoid arthritis, and systemic lupus erythematosus.⁶

In two reports,^{3,4} in contrast to those already mentioned, there does appear to be post-mortem evidence for intracranial involvement of smaller cerebral vessels. However, in one of these reports the findings relate to minor changes in small vessels (with dubious symptomatic consequences),³ and in the other instance the clinical features are not entirely characteristic of GCA and another diagnosis cannot be excluded.⁴ Such changes may in fact be the result of other conditions such as polyarteritis nodosa, Buerger's disease (endarteritis obliterans), tuberculosis, and Takayasu's syndrome (pulseless disease).⁷ In these four conditions giant cells with inflammatory changes have been noted in pathological specimens, but clinical symptoms and signs help to differentiate them from GCA. However, signs and symptoms occasionally overlap owing to similar sites of involvement.⁷

A considerable literature tends to support our findings.^{11-16, 18} Extracranial vertebral artery and internal carotid artery involvement has been noted, giving rise to cerebral manifestations either through thromboembolic episodes, direct extension of thrombus from the site of arteritis into the artery of supply, or by reduced vertebral artery perfusion aggravated by concomitant arteritic or non-arteritic involvement of the internal carotids or insufficiency of the circle of Willis.

The vertebral arteritic changes reported by Crompton³ and Wilkinson and Russell¹² were noted to have a sharply defined upper border about 5 mm above the point of dural perforation. The terminal segment of the internal carotid artery within the dura was never involved.¹²⁻¹⁴ This was thought to reflect the close correlation between susceptibility of GCA and the amount of elastic tissue in the media and adventitia of the individual arteries of the head and neck, as GCA is thought to be an autoimmune reaction involving arterial elastic tissue. Major transformation in the arterial muscle coats occurs as they enter the skull, with a gross diminution in the amount of elastic tissue. Intracranial arteries may be spared owing to the presence of little or no elastic tissue in their coats.¹² This would also explain our

pathological findings in the optic nerves, which showed infarction in the retrolaminar region due to GCA affecting the posterior ciliary arteries. In both of our post-mortem examinations the central retinal vessels were patent.

Cullen¹⁹ and MacFaul²⁰ have reported in another case a similar picture of involvement of the posterior ciliary arteries and of the origin of the central retinal artery outside the globe and outside the optic nerve. The central retinal artery within the optic nerves as well as the retinal vessels within the globe and the choroidal vessels were all patent. This is important in view of the fact that the wall of the central retinal artery within the optic nerve contains very little elastic tissue (in contrast to considerably more in the walls of the ophthalmic and posterior ciliary arteries,¹² and the internal elastic lamina ceases as the central retinal artery emerges from the disc.

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- 1 Save-Soderbergh J, Malmvall BE, Anderson R, Bengtsson BA. Giant-cell arteritis as a cause of death. *JAMA* 1986; 255: 493-6.
- 2 Kjeldsen MH, Reske-Nielsen E. Pathological changes of the central nervous system in giant-cell arteritis. *Acta Ophthalmol (Kbh)* 1967; 46: 49-56.
- 3 Crompton MR. The visual changes in temporal (giant-cell) arteritis. *Brain* 1959; 82: 377-90.
- 4 McCormick HM, Neuburger KT. Giant-cell arteritis involving small meningeal and intracerebral vessels. *J Neuropathol Exp Neurol* 1958; 17: 471-8.
- 5 Morrison AN, Abitbol M. Granulomatous arteritis with myocardial infarction: a case report with autopsy findings. *Ann Intern Med* 1955; 42: 691-700.
- 6 Hirach M, Mayersdorf A, Lehmann E. Cranial giant cell arteritis. *Br J Radiol* 1974; 47: 503-6.
- 7 Heptinstall RH, Porter KA, Barkley H. Giant-cell (temporal) arteritis. *J Pathol* 1954; 67: 507-18.
- 8 Gilmour JR. Giant-cell chronic arteritis. *J Pathol* 1941; 53: 263-77.
- 9 McMillan GC. Diffuse granulomatous aortitis with giant cells. *Arch Pathol* 1950; 49: 63-9.
- 10 Hinck VC, Carter CC, Rippey JG. Giant-cell cranial arteritis: a case with angiographic abnormalities. *AJR* 1964; 92: 769-75.
- 11 Meadows SP. Temporal or giant-cell arteritis. *Proc R Soc Med* 1966; 59: 329-33.
- 12 Wilkinson I, Russell RW. Arteries of the head and neck in giant cell arteritis. *Arch Neurol* 1972; 27: 378-91.
- 13 Spencer WH, Hoyt WF. A fatal case of giant-cell arteritis with ocular involvement. *Arch Ophthalmol* 1960; 64: 862-7.
- 14 Chisholm IH. Cortical blindness in cranial arteritis. *Br J Ophthalmol* 1975; 59: 332-3.
- 15 Symonds C, Mackenzie I. Bilateral loss of vision from cerebral infarction. *Brain* 1957; 80: 415-53.
- 16 Monteiro LRM, Coppeto JR, Greco P. Giant-cell arteritis of the posterior cerebral circulation presenting with ataxia and ophthalmoplegia. *Arch Ophthalmol* 1984; 102: 407-9.
- 17 Nordberg E, Bengtsson BA. Death rates and causes of death in 284 consecutive patients with GCA confirmed by biopsy. *BMJ* 1989; 229: 549-50.
- 18 Cullen JF. Temporal arteritis: occurrence of ocular complications 7 years after diagnosis. *Br J Ophthalmol* 1972; 56: 584-8.
- 19 Cullen JF. Occult temporal arteritis. *Trans Ophthalmol Soc UK* 1963; 83: 725-36.
- 20 MacFaul PA. Ciliary artery involvement in giant cell arteritis. *Br J Ophthalmol* 1967; 51: 505-12.

Fuchs's heterochromic cyclitis in congenital ocular toxoplasmosis

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Abstract

We report a follow-up after 25 years of a patient with a congenital bilateral ocular toxoplasmosis who developed Fuchs's heterochromic cyclitis in her left eye. Whether *Toxoplasma gondii* can cause the development of Fuchs's heterochromic cyclitis, as our case suggests, or whether the iridocyclitis is a secondary ocular response to other agents, is not yet clear.

Although Fuchs's heterochromic cyclitis is a distinct disease, the specific cause is still unknown. An association between it and ocular toxoplasmosis is assumed because of the presence of chorioretinal scars in 7.5%–60% of patients, which are consistent with a previous intraocular toxoplasmosis.^{1,2} Apart from these toxoplasma-like scars, non-specific chorioretinal lesions are also described.³

Two theories explaining the association between the fundus lesions and Fuchs's cyclitis have been proposed. First, the fundus lesions in these patients are due to a previous toxoplasma infection. Secondly, the scars are of non-toxoplasma origin and may result from antibodies produced during the course of anterior segment inflammation (cross reacting with pigment bearing cells in the uvea and fundus). Until now only sporadic cases of Fuchs's disease with an active toxoplasma lesion or a well documented history of active ocular toxoplasmosis have been reported.^{1,2} We now report, after a follow-up of 25 years, on a patient with a congenital bilateral ocular toxoplasmosis who developed unilateral Fuchs's heterochromic cyclitis.

Case report

A 4-week-old female child was seen by an ophthalmologist because of suspected congenital toxoplasmosis. Her mother had had a seroconversion in the last trimester of pregnancy (Sabin-Feldman dye test titre 1:16 384). The patient was prematurely born (gestation time: 31 4/7 weeks, weight 1790 g). Paediatric and neurological examinations revealed no apparent abnormalities. She had a positive Sabin-Feldman dye test (titre 1:256). On ophthalmic examination the child had slight microphthalmus of the right eye (cornea diameter on the right 8 mm, 9.5 mm on the left) and pigment on the lens. No abnormalities were seen in the fundus. At the age of 4½ months the dye test titre had increased (titre 1:4096) and the patient had developed splenomegaly. An electroencephalogram, made when she was 8 months old, showed a slightly abnormal pattern which could be consistent with a diffuse encephalopathy. We diagnosed con-

genital toxoplasmosis on the seroconversion in her mother in the last trimester of pregnancy, the increase in antitoxoplasmal antibodies during the first months of the patients' life, and on the clinical picture.

When the patient was 11 years old she consulted an ophthalmologist because of blurred vision in her left eye. Her visual acuity was 20/60 on the right and 20/15 on the left. In addition to the microphthalmus old atrophic hyperpigmented scars compatible with toxoplasmosis were seen in the right fundus. Examination of her left eye disclosed two active peripheral lesions of focal retinochoroiditis and a mild iritis. Both the Sabin-Feldman dye test (titre 1:64) and the complement binding reaction (titre 1:4) were low positive. The diagnosis of active ocular toxoplasmosis was made, and the patient was treated with atropine and corticosteroids drops. Owing to the peripheral localisation of the inflammatory focus, systemic therapy was considered to be not required. Within several weeks the retinal lesions sharpened and ultimately became atrophic hyperpigmented scars.

Two years later the patient returned to the ophthalmologist with complaints of floaters in her left eye (visual acuity 20/60 on the right and 20/15 on the left). Ophthalmic examination of the left eye revealed fine white keratic precipitates, scattered on the entire endothelium. Heterochromia with the left iris clearly lighter than the right iris and the absence of synechiae were noted (Fig 1); in addition sporadic cells in the aqueous and evident vitreous opacities were observed. Fundus examination of both eyes showed old known atrophic scars; active lesions were not present (Fig 2). Tests to exclude other causes of uveitis (serum angiotensin converting enzyme, serum lysozyme, serological tests for syphilis, Mantoux test, chest x ray) were all within normal range. Based on the clinical picture our diagnosis was Fuchs's heterochromic cyclitis. From the age of 13 years the patient did



Figure 1 Evident heterochromia in a patient with bilateral congenital ocular toxoplasmosis and Fuchs's heterochromic cyclitis of her left eye.

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Figure 2A Old atrophic hyperpigmented chorioretinal scars compatible with toxoplasmosis in the right eye.

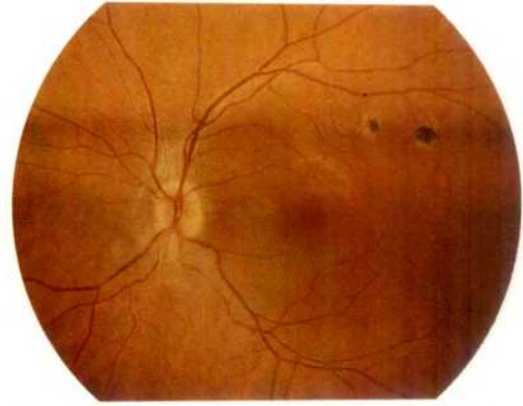


Figure 2B Chorioretinal scars of toxoplasma origin in the left eye with Fuchs's heterochromic cyclitis.

not suffer another recurrence of ocular toxoplasmosis. Only the fluctuation in intensity of vitreous opacities, characteristic of Fuchs's heterochromic cyclitis, has caused her to visit the ophthalmologist in the past 12 years.

Discussion

We report this case to help to elucidate the association between Fuchs's heterochromic cyclitis and ocular toxoplasmosis. During a follow-up of 25 years, starting when our patient was 4 weeks old, we recorded the appearance of active toxoplasma lesions in the left retina when the patient was 11 years old and again two years later. A clinical picture characteristic of Fuchs's heterochromic cyclitis then developed in the same eye. Until now only cases of presumptive ocular toxoplasmosis with clinical features of Fuchs's heterochromic cyclitis have been described. This report describes the development of Fuchs's heterochromic cyclitis in a patient with definite congenital ocular toxoplasmosis. The case suggests that infection with *Toxoplasma gondii* may cause the development of Fuchs's heterochromic cyclitis.

Whether Fuchs's iridocyclitis is a secondary response to a variety of different aetiological agents is not yet clear.⁴ Associations between it and other ocular diseases have been reported – retinitis pigmentosa, trauma, scars of non-toxoplasma origin.^{2,3,5} Moreover recent immunohistochemical analysis of iris biopsy specimens in these patients has failed to show any specific immunohistological abnormality.⁶ It is therefore conceivable that Fuchs's heterochromic cyclitis may be a single clinical entity with different causes.

- 1 De Abreu ML, Belfort R, Hirata PS. Fuchs's heterochromic cyclitis and ocular toxoplasmosis. *Am J Ophthalmol* 1982; 93: 739–44.
- 2 Saraux H, Laroche L, Le Hoang P. Secondary Fuchs's heterochromic cyclitis: a new approach to an old disease. *Ophthalmology* 1985; 190: 193–8.
- 3 Arffa RC, Schlaegel TF. Chorioretinal scars in Fuchs's heterochromic iridocyclitis. *Arch Ophthalmol* 1984; 102: 1153–5.
- 4 Nussenblatt RB, Palestine AG. Fuchs's heterochromic iridocyclitis. In: Nussenblatt RB, Palestine AG, eds. *Uveitis. Fundamentals and clinical practice*. Chicago: Year Book Medical Publishers, 1989: 176–8.
- 5 Vourre I, Saari M, Tilikainen A, Rasanen O. Fuchs's heterochromic cyclitis associated with retinitis pigmentosa: a family study. *Can J Ophthalmol* 1979; 14: 10–6.
- 6 Murray PI, Mooy CM, Visser-de Jong E, et al. Immunohistochemical analysis of iris biopsy specimens from patients with Fuchs's heterochromic cyclitis. *Am J Ophthalmol* 1990; 109: 394–9.

Case of penetrating orbitocranial injury caused by wood

Erkan Mutlukan, Brian W Fleck, James F Cullen, Ian R Whittle

Abstract

A case of retained intraorbital and intracerebral wooden foreign body following an orbitocranial penetrating injury through the lower lid of an adult is described. Initial failure to recognise the true nature of the injury led to intracerebral abscess formation and monocular blindness. Diagnosis and management of such cases are discussed.

A fit 41-year-old male presented with a blunt injury to the right eye, and lacerations of the lower eyelid. He had fallen from a fence into some wooden foliage, but had not been concussed.

On examination the visual acuity was 20/30 in the right eye and 20/20 in the left. Two splinters of wood were removed from small lacerations in the right lower eyelid. There was a slight ptosis. A 10 mm conjunctival laceration was present just inferior to the cornea. The sclera was intact. Abduction of the eye was normal, but all other ocular movements were limited. Corneal hypoesthesia and a hyphaema were present, and the intraocular pressure was 50 mmHg. The pupil was oval, but reacted normally. The fundus was normal, as was the visual field to confrontation. The left eye was healthy. A skull x ray did not show any abnormality.

The patient was admitted to an ophthalmology ward. The conjunctival and cutaneous lacerations were sutured, and oral acetazolamide was given to control the intraocular pressure.

Six hours later the patient became pyrexial, with a temperature of 39°C, and his conscious level deteriorated to Glasgow Coma Scale 9. He was therefore transferred to the regional neurosurgery department.

An extradural haematoma was suspected, and a CT scan was performed. It showed right sided frontal lobe contusions with associated subarachnoid and intracerebral haemorrhage (Fig 1). Air was evident in the right orbit and adjacent to the intracerebral haematoma. A right frontal burr hole was made, which revealed contused cortex and subarachnoid haemorrhage. A subdural catheter was therefore inserted to monitor intracranial pressure. Microbiological examination of the catheter swab identified a *Fusobacterium* sp. and *Leptotrichia buccalis*.

The patient's pyrexia resolved with antibiotic treatment and his conscious level gradually improved to GCS 15. However, he gradually developed a right proptosis, measuring 25 mm in the right eye (17 mm in the left) during the next five days. His visual acuity was reduced to hand movements, and a right afferent pupil defect developed. A repeat CT scan showed a mass situated superiorly and medially in the right orbit, thickening of the medial rectus muscle, and an orbital roof fracture (Figs 2, 3, 4). In addition a right frontal haematoma with surrounding oedema was present (Fig 5).

An emergency right frontal craniotomy, right optic canal decompression, and exploration of the right orbit were therefore performed through a superior orbitotomy. This revealed an abscess

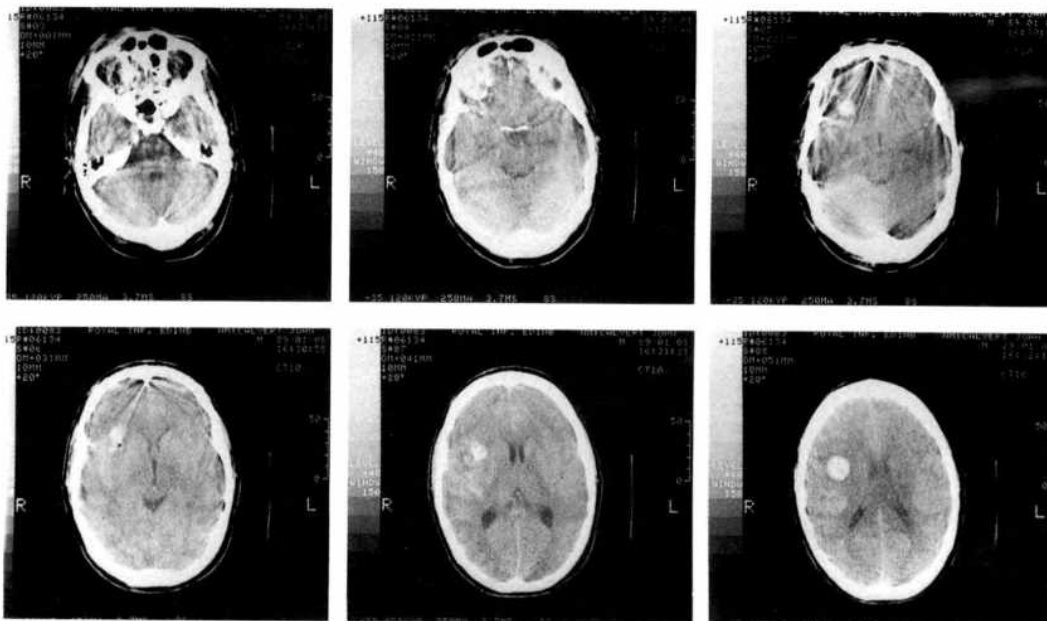


Figure 1 CT scan on the day of admission showed right frontal contusion with associated subarachnoid and intracerebral haemorrhage. Air was evident in the right orbit and intracranially.

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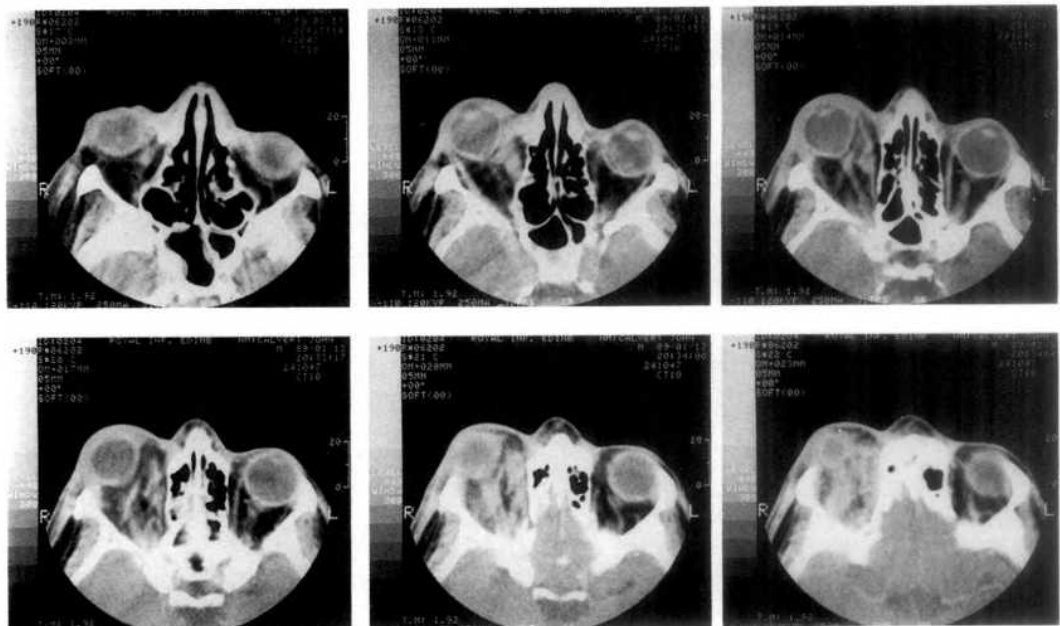


Figure 2

Figure 2, 3, 4 A repeat CT scan on the fifth day after injury showed a right intraorbital mass extending superiorly and medially in the right orbit, associated with thickening of the medial rectus muscle and an orbital roof fracture.

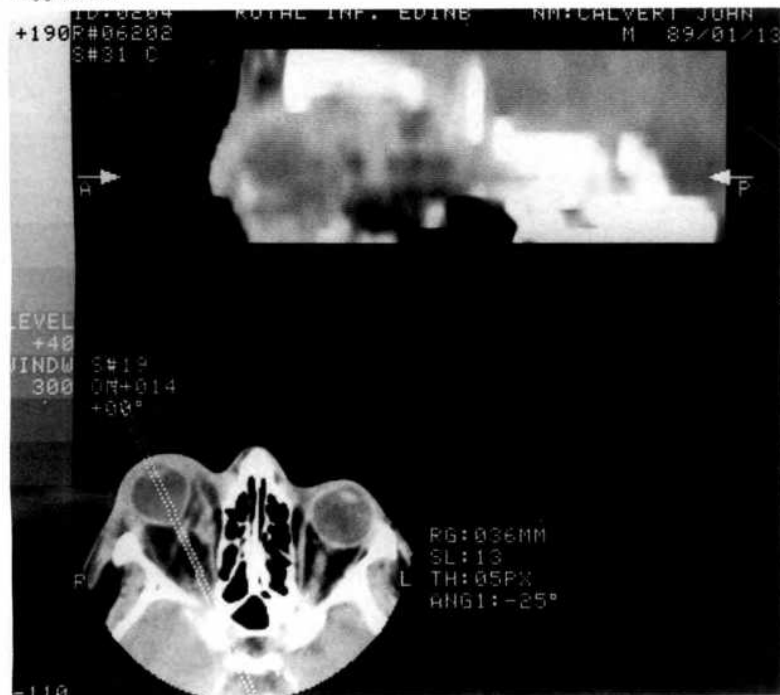


Figure 3

cavity which contained fragments of wood in the right frontal lobe. Multiple fragments of wood were also found in the posterior and inferomedial parts of the orbit. Pus from the brain abscess grew *Bacteroides asaccharolyticus* and small numbers of anaerobes.

Postoperatively the patient developed focal seizures, which responded to treatment with phenytoin. Further aspiration of the right frontal lobe abscess was performed with CT-imaged guided stereotaxy five weeks later. At the time of most recent follow-up the ptosis and exophthalmos had completely resolved, with full ocular movements, but the visual acuity in the right eye was no perception of light and optic atrophy had developed. There was no other neurological deficit.

Discussion

This case serves as a reminder that seemingly trivial injuries of the eyelids can be associated with severe lesions in the orbital region and shows the need to suspect intracranial penetration in orbital injuries.¹⁻⁷

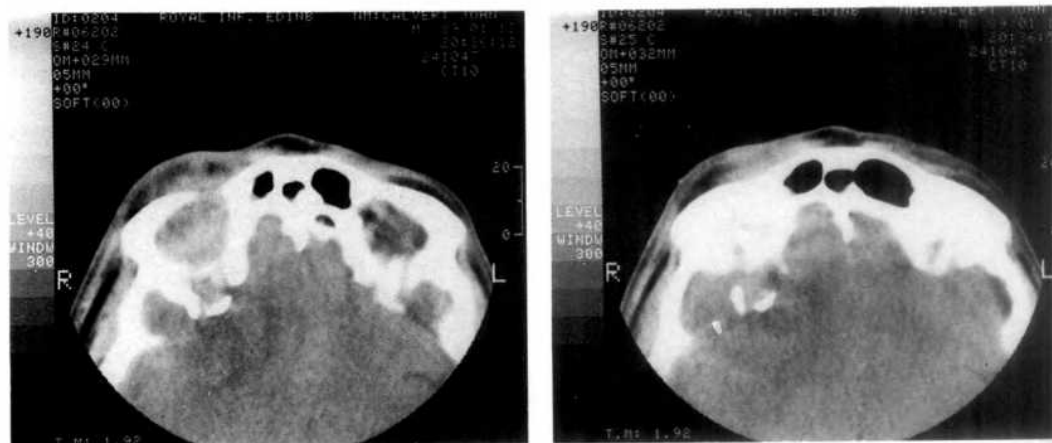


Figure 4

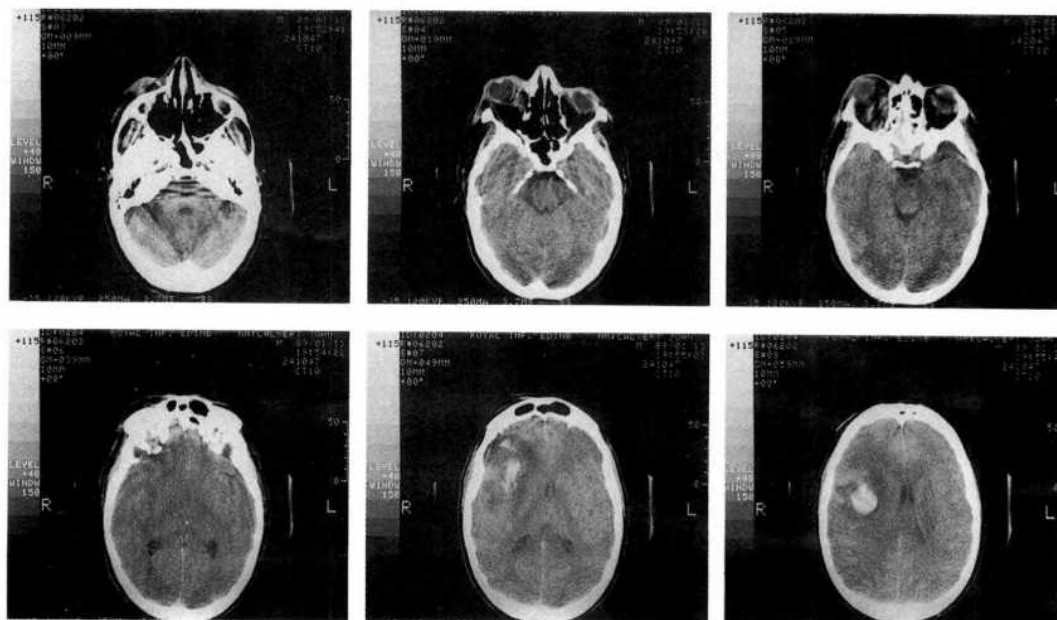


Figure 5 The right frontal intracerebral haematoma has prominent surrounding oedema five days after the injury.

Transorbital intracranial penetration by a wooden foreign body is unusual. Previous cases with entry sites at the upper lid, inner or outer canthus, and without any ocular damage, as well as other types of orbitocranial injuries have been reported.^{1-6,12} We are unaware of any previous report of wooden foreign body penetration into the cranial cavity through the lower lid and orbital roof in the absence of perforation of the globe. Wood is not detected on plain x rays and very difficult to detect on CT scans, as it has a density very similar to that of intracranial and orbital soft tissue, especially after being present in an aqueous environment for 48 hours, when it has had time to absorb fluid.¹³⁻¹⁵ Ultrasound often does not detect orbital wood if it is dry and surrounded by air in the cavity.¹⁶ The value of magnetic resonance imaging in detecting intra-orbital wood has recently been reported, and MRI scanning has been advocated when penetration by a wooden foreign body and its retention are suspected.^{6,17}

All periorbital puncture wounds should alert the physician to the possibility of intracranial penetration. Intensive antibiotic therapy must be started immediately after all perforating orbital wounds by wooden objects even in the absence of any systemic and neurological signs, as the porous organic nature of the wood provides a dangerous natural reservoir for micro-organisms, causing a 12.5–25% mortality rate secondary to intracranial infection.^{5,11,18} Antibiotics alone may not suffice, and there is a need for expeditious and

thorough surgical exploration if retention of a wooden foreign body is suspected.

- 1 Gunkelch AN. Apparently trivial wounds of the eyelids with intracranial damage. *Br Med J* 1960; ii: 842–4.
- 2 Broch L, Tenenbaum HL. Retention of wooden foreign bodies in the orbit. *Can J Ophthalmol* 1980; 15: 70–2.
- 3 Macrae JA. Diagnosis and management of a wooden orbital foreign body: case report. *Br J Ophthalmol* 1979; 63: 848–51.
- 4 Horner FA, Berry RG, Frantz M. Broken pencil points as a cause of brain abscess. *N Engl J Med* 1964; 271: 342–5.
- 5 Webster JE, Schneider RC, Lofstrom JE. Observations upon the management of orbitocranial wounds. *J Neurosurg* 1946; 3: 329–36.
- 6 Yamashita T, Kadota K, Asakura T, Ohba N. Penetrating orbitocranial injury: report of a case by a chopstick. *Orbit* 1988; 7: 59–64.
- 7 Schneider RC, Henderson JW. Penetrating orbital wound with intracranial complications. *Arch Ophthalmol* 1952; 47: 81–5.
- 8 Duffy GP, Bahandari YS. Intracranial complications following transorbital penetrating injuries. *Br J Surg* 1969; 56: 685–8.
- 9 Albert DM, Burns WM, Scheie HG. Severe orbitocranial foreign body injury. *Am J Ophthalmol* 1965; 60: 1109–11.
- 10 Bowen DI. Self inflicted orbitocranial injury with a ball point plastic pen. *Br J Ophthalmol* 1971; 55: 427–30.
- 11 Bard LA, Jarrett WH. Intracranial complications of penetrating orbital injuries. *Arch Ophthalmol* 1964; 71: 332–43.
- 12 Bursick DM, Selker RG. Intracranial pencil injuries. *Surg Neurol* 1981; 16: 427–31.
- 13 Tate E, Cupples H. Detection of orbital foreign bodies with computed tomography: current limits. *AJR* 1981; 137: 493–5.
- 14 Myllyla V, Pyhtinen J, Pajvansalo M, et al. CT detection and location of intraorbital foreign bodies: experiments with wood and glass. *ROFO* 1987; 146: 639–43.
- 15 Kuhns LR, Borlaza GS, Seigel RS, et al. An in-vitro comparison of computed tomography, xero-radiography and radiography in the detection of soft-tissue foreign bodies. *Radiology* 1979; 132: 218–9.
- 16 McQuown DS. Ocular and orbital echography. *Radiol Clin North Am* 1975; 13: 523–41.
- 17 Green BF, Kraft SP, Carter KD, et al. Intraorbital wood detection by magnetic resonance imaging. *Ophthalmology* 1990; 97: 608–11.
- 18 Miller CF II, Brodkey JS, Colombi BJ. The danger of intracranial wood. *Surg Neurol* 1977; 7: 95–103.

Visual field changes following hepatic transplantation in a patient with primary biliary cirrhosis

R H B Grey

Abstract
A case of severe visual field restriction complicating primary biliary cirrhosis is described. The clinical features demonstrated vitamin A deficiency which did not respond to oral supplements of vitamin A. Hepatic transplantation restored the visual fields to near normal.

A 51-year-old woman was referred to the Bristol Eye Hospital by her general practitioner. She was known to be suffering from primary biliary cirrhosis for five years and was persistently jaundiced. For several months prior to her referral she had been aware of gradual deterioration of vision in her left eye. She had no relevant past ophthalmic history. She was on treatment for biliary cirrhosis and was receiving intramuscular vitamin A, D, and K replacement. She was also taking oral loperamide, spironolactone, terfenadine, and cholestyramine.

Ocular examination showed her visual acuities were 6/9, N 8, in the right eye and 6/18, N 10 in the left eye. The anterior segments were normal, but both fundi showed small discrete retinal pigment epithelial lesions extending from the posterior pole to the equator. Some spots were intensely white and well demarcated, whereas others, particularly those in the periphery, were paler with soft edges (Figs 1A, B). The peripheral visual fields were markedly constricted to less than 10° bilaterally (Fig 2A). 100-Hue testing showed error of scores of 71 in the right eye and 237 in the left eye, with a tritan axis in each eye.

Fluorescein angiography showed slight masking of the background choroidal fluorescence by the pigment epithelial spots in the early stages of the run, progressing to slight

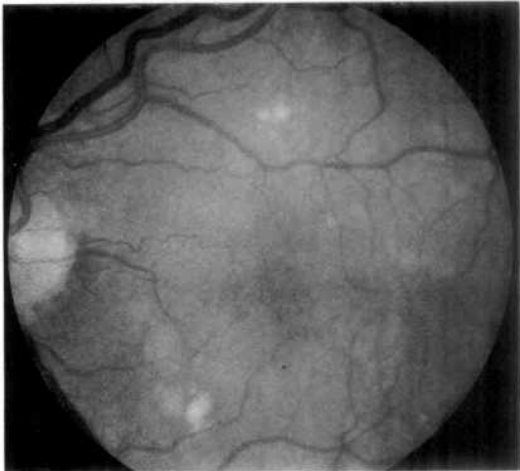


Figure 1A



Figure 1B

Figure 1 A and B Preoperative appearance with multiple white punctate lesions of variable density throughout the fundi of both eyes.

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Table 1 Electrophysiological, colour vision, and serological data

White light	ERG	Blue light	ERG	VEP		EOG		100 Hue		Serum bilirubin	Serum alkaline phosphatase	
Amplitude: μV		Amplitude: μV			Amplitude: μV					$\mu mol/l$	IU	
Photopic	Scotopic	11 min	DA	30 min DA	R	L	R	L	R	L		
Pretransplant												
(a) 4.5	9.5	—	—	—	11.5	8.5	235	200	71	237	346	1071
(b) 8.5	21.0	2.0	—	14.0								
Post-transplant												
(a) 4.0	6.5	—	—	—	6.0	6.0	244	250	52	151	18	105
(b) 8.5	21.0	2.0	—	7.0								
Normal values												
(a) 5.6 (SD 2.1)	5.6 (SD 2.1)	—	—	—	>3.0		>170		—		2–20	20–110
(b) 7.6 (SD 3.1)	27.3 (SD 11.1)	8.5–12.5	—	11.5–27.5								

ERG and VEP latencies all normal. (a)=a wave. (b)=b wave. DA=dark adaptation. R=right eye. L=left eye.

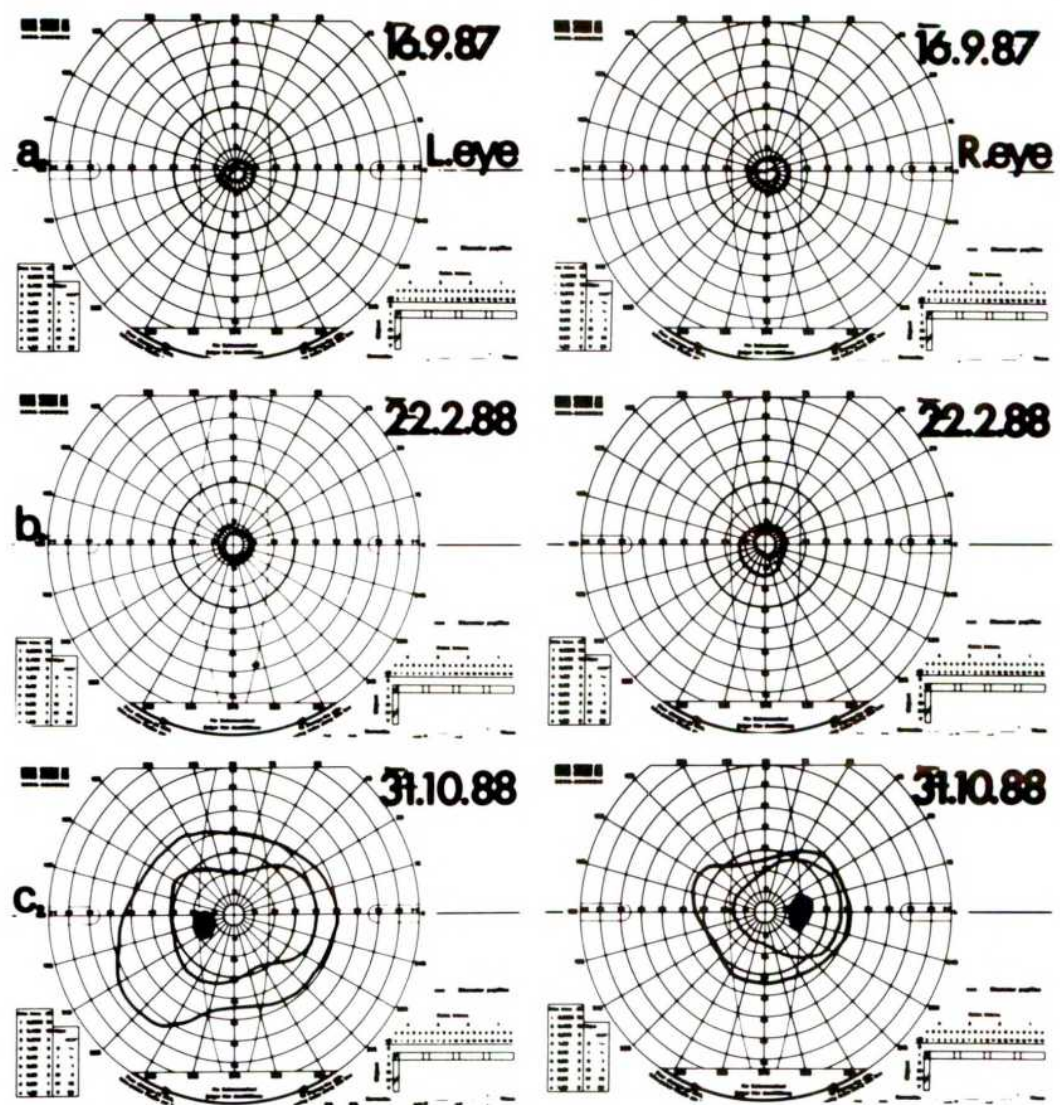


Figure 2 (a) Goldmann fields at presentation. (b) Goldmann fields after intramuscular vitamin A supplements increased. (c) Goldmann fields after transplantation.

staining of lesions from the late venous phase onwards. A few spots showed intense staining (Figs 3A, B).

Electrophysiological studies showed delayed dark adaptation. The B wave of the electroretinogram (ERG) to blue flashes of light was

reduced in the early stages but reached normal levels after 30 minutes. The ERG to white light and the electro-oculogram (EOG) were normal. The methods used for electrophysiological testing have been described in detail.^{1,2} The EOG was recorded after a 10-minute period of dark

Figure 3 A and B Early and late stages of fluorescein angiogram showing initial masking of choroidal fluorescence and subsequent staining of the pigment epithelium.

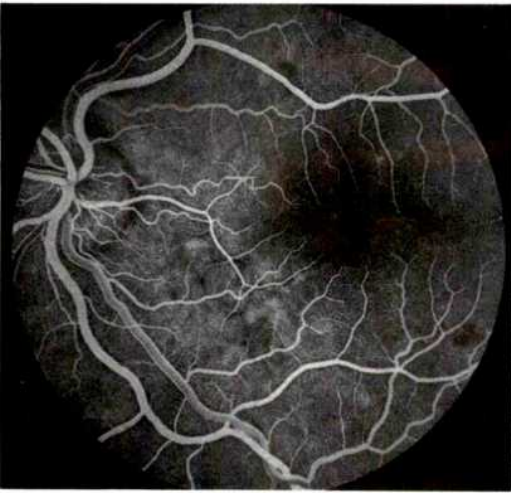


Figure 3A

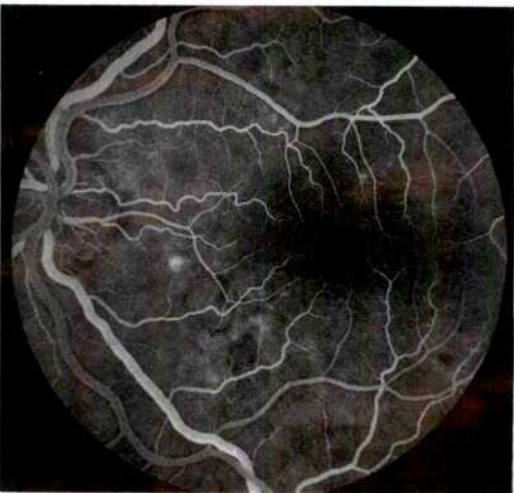


Figure 3B

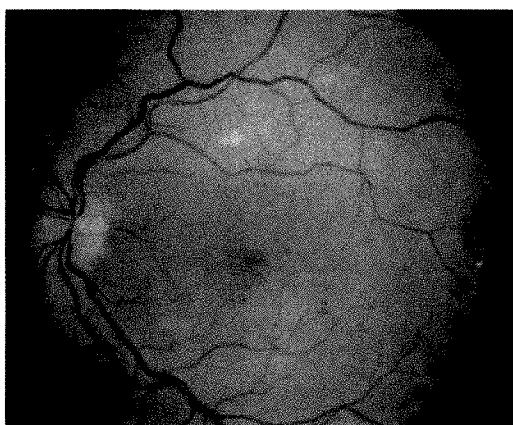


Figure 4 Postoperative fundus appearance showing partial resolution of punctate lesions.

adaptation followed by exposure to bright light (3000 cd/m^2). The ERG was measured with skin electrodes and stroboscopic flashes at 1-second intervals 30 cm in front of the patient. Initially patients were light adapted in normal room illumination for 15 minutes, following which the lights were extinguished. Recordings were taken immediately and at 5 minutes for white light and at 7 and 30 minutes for blue light (stimulus reduced by 2 log units by the filter).

The fundus changes were consistent with vitamin A deficiency. Serum vitamin A was measured and found to be 0.8 mmol/l (normal 1.1 to 3.5). The vitamin A dosage was increased from $300\,000$ units monthly to $300\,000$ units weekly and the serum vitamin A level increased to 1.8 mmol/l . Subjectively her vision improved. Her visual acuities in February 1988 were 6/9 right and left, but her visual fields remained essentially unchanged at approximately 10° (Fig 2B).

The patient's general condition deteriorated, with increased jaundice, anorexia, and weight loss, and hepatic function became grossly abnormal (Table 1). In April 1988 she underwent hepatic transplantation, which produced rapid improvement in her general health and restoration of normal hepatic function. Reassessment of her visual function six months later showed considerable improvement in her visual fields (Fig 2C) and 100-hue tests, with reduction of the tritan axis. However, her fundal appearances showed that the white lesions had persisted but were fainter (Fig 4). The blue flash ERG remained unchanged with delayed dark adaptation. At follow-up 18 months after transplantation her visual acuities and fields remained stable.

Discussion

Primary biliary cirrhosis is thought to be an autoimmune disease causing destruction of the small intrahepatic bile ducts. There is an association with other autoimmune diseases, and frequently a high serum IgM and circulating immune complexes are found. Antimitochondrial antibodies are seen in over 90% of cases. The patients are usually female and aged 40–60 years, and the disease produces pruritus, steatorrhoea, weight loss, and hepatosplenomegaly. The development of jaundice is

considered a poor sign for survival, indicating progressive liver failure. Vitamin deficiencies are well recognised, particularly of vitamins D and K, but approximately a quarter of patients have a low serum vitamin A level.³ The patient under discussion showed all the typical findings.

Chronic liver disease may produce sufficient vitamin A deficiency to induce ocular complications: nyctalopia, peripheral visual field restriction, white punctate retinal pigment epithelial lesions, loss of dark adaptation, and reduction in the values of the EOG and scotopic ERG have been described.^{3–11} The mechanism of these effects is presumed to be poor absorption through the gut. Reduced bile acids in the intestinal tract impair absorption of lipids and fat soluble vitamins, including vitamin A. Chronic liver disease may also decrease the production of retinol binding protein and pre-albumin, which are necessary for vitamin A transport to the retinal pigment epithelium. Plasma proteins were normal in this patient, though retinol binding protein was not measured specifically.

Previous reports have suggested that intramuscular vitamin A supplements reverse the visual field and electrophysiological changes, though the fundus appearance remains abnormal.^{3–5,8,11} Walt *et al*⁸ recommended that in primary biliary cirrhosis vitamin A is more effective by mouth than by intramuscular injection. Parenteral administration bypasses the normal hepatic delivery and esterification of vitamin A following gut absorption, and it may therefore reduce its efficacy. In the present case injections of vitamin A did not produce significant functional improvement in spite of several weeks of normal plasma vitamin A levels, whereas hepatic transplantation caused a rapid restoration of peripheral field. The outcome in this patient would support this theory.

Functional amblyopia was considered unlikely in view of her precise consistency on repeated field testing, physical changes in the pigment epithelium, and abnormal electrophysiological findings.

Colour vision abnormalities have not been described before in primary biliary cirrhosis, and though not severe in this patient there was a notable change after transplantation. This may suggest that photopic photochemistry, like scotopic photochemistry, has some degree of dependency on liver metabolism.

ERG or EOG abnormalities have been described as the first indication of abnormal retinal function in vitamin A deficiency, but the electrophysiological changes in this case were remarkably small compared with the functional field deficit and fundus appearances. It is also interesting that the mild delay in dark adaptation persisted along with the fundus abnormalities in spite of the improvement in visual fields after transplantation. Prolonged hypovitaminosis has the capacity to induce some degree of permanent structural and functional damage to the photoreceptor-pigment epithelial complex, but treatment leads to considerable improvement.

My thanks are expressed to Dr D Papakostopoulos for performing the electrophysiological tests, Mrs Gill Bennerson for photographic help, and Mrs Linda Clayton for typing the manuscript.

- 1 Papakostopoulos D. Clinical electrophysiology of the human visual system. In: Chiarenza GA, Papakostopoulos D, eds. *Clinical application of cerebral evoked potentials in paediatric medicine*. Amsterdam: Excerpta Medica, 1982: 3-40.
- 2 Papakostopoulos D, Dean Hart C, Cooper R, Natsikos V. Combined electrophysiological assessment of the visual system in central serous retinopathy. *Electroencephalogr Clin Neurophysiol* 1984; 59: 77-80.
- 3 Elta GH, Furie BC, Furie B, Jacob R, Russell RM, Kaplan MM. Fat soluble vitamins in primary biliary cirrhosis. *Hepatology* 1982; 2: 703.
- 4 Bors F, Fells P. Reversal of complications of self induced vitamin A deficiency. *Br J Ophthalmol* 1971; 55: 210-4.
- 5 Russell RM, Morrison SA, Smith FR, Oaks EV, Carney EA. Vitamin A reversal of abnormal dark adaptation in cirrhosis. *Ann Intern Med* 1978; 88: 622-6.
- 6 Sommer A, Tjakrasudjatma S, Junaedi E, Green WR. Vitamin A responsive panocular xerophthalmia in a healthy adult. *Arch Ophthalmol* 1978; 96: 1630-4.
- 7 Herlong HF, Russell RM, Maddrey WC. Vitamin A and zinc therapy in primary biliary cirrhosis. *Hepatology* 1981; 1: 348-51.
- 8 Walt RP, Kemp CM, Lyness L, Bird AC, Sherlock S. Vitamin A treatment in night blindness in primary biliary cirrhosis. *Br Med J* 1984; 288: 1030-1.
- 9 Shepherd AN, Bedford GJ, Hill A, Bouchier IAD. Primary biliary cirrhosis, dark adaptometry electro-oculography and vitamin A state. *Br Med J* 1984; 284: 1484-5.
- 10 Kaplan MM. Primary biliary cirrhosis. *N Engl J Med* 1987; 316: 521-8.
- 11 O'Donnell M, Talbot JF. Vitamin A deficiency in treated cystic fibrosis - a case report. *Br J Ophthalmol* 1987; 71: 787-90.

FIFTY YEARS AGO

Mustard gas and its implications

DEAR SIRS,—In reply to Messrs. John Eyre and Frank W Law may I state that I have seen one drop of 4 per cent solution of hyd. perchlor. in glycerine accidentally fall on the cornea and in a few seconds which elapsed before washing out the conjunctival sac, severe and lengthy, but not permanent damage was inflicted on almost the whole of the corneal epithelium. Here there was no question of absorption. I quite agree with them that in the field of biology there is nothing more misleading than the argument from analogy, which indeed led eminent men to assume and publish results on the assumption that because man could accommodate the mammals could also.

But the argument from analogy hardly applies in this instance just quoted.

As regards the late effects of mustard gas on the cornea, the few cases I have seen showed deep seated infiltration rather than ulceration and there was very little clear cornea left anywhere. So that I doubt whether either diathermy or contact glasses would

have assisted. If such cases, which I am glad to say are rare, present themselves, the method suggested will be borne in mind. It is true that these conditions do recur without obvious cause. No one will be more grateful than myself if the writers have devised an effective treatment of mustard gas in the field, and will look forward to their publication of their experimental results. But the practical use of any remedy of the kind in advanced positions of any army is very difficult but not insuperable.

Some idea of the difficulty of acting efficiently in advanced stations may be learnt from the Palestine campaign, where towards the end men with high temperature were given quinine at once, no matter what seemed to be the cause of the temperature. If the medical officers had waited until they could be sure that malaria was the cause it would at times have been too late. To neutralise the effects of mustard on the eyes, special instruction for the forward units will be a necessity. — Letter from James W Barrett.

Br J Ophthalmol 1941; 25: 95.

Vitreotomy, argon laser, and gas tamponade for serous retinal detachment associated with an optic disc pit: a case report

M P Snead, N James, P M Jacobs

Abstract

We report the case of a 9-year-old boy with a right optic disc pit and associated serous retinal detachment of the macula. This was treated by vitrectomy, endolaser, and gas tamponade as a primary procedure, which resulted in complete resolution. We review the literature and conclude that further reports of the management of this uncommon condition are required so that firmer guidelines on treatment can be established.

A 9-year-old Caucasian boy presented to the eye casualty department in July 1989 with a six-month history of decreased visual acuity. A year previously an optician had recorded unaided visual acuities of 6/6 right eye and 6/6 left eye. There was no relevant past ocular or medical history of note.

On examination his unaided visual acuities were 6/6 left and 1/60 right eye. There was no improvement with refraction. The anterior segment appeared normal, he had a right relative afferent pupil defect, and funduscopy revealed a serous retinal detachment of the macula clearly linked to an optic disc pit in the right eye. The detached retina had undergone cystic retinal degeneration, and the underlying pigment epithelium was irregularly pigmented (Fig 1). The left fundus was normal. The patient thought that there had been a recent improvement in the vision of the right eye, and treatment was therefore deferred and serial observations carried out. After nine months no further improvement had occurred. Various methods of treatment (see 'Discussion') were considered, and, though laser photocoagulation alone has met with some success, in view of the patient's age this would



Figure 2 Postoperative fundus photograph.

have required a general anaesthetic. Vitrectomy and laser photocoagulation followed by fluid/gas exchange seemed to offer the highest chance of success with a single procedure (and anaesthetic), and it was agreed to proceed with surgery.

On 10 April 1990 the patient underwent right pars plana vitrectomy, endolaser treatment, and 40% SF₆ exchange. A standard 20 g three-port pars plana vitrectomy was performed, and during surgery the vitreous was noted to be still attached. Argon endolaser was applied temporal to the disc in a confluent double line of burns to seal off the link between pit and detachment and extended superiorly and inferiorly into attached retina. This was applied after the vitrectomy and before fluid-gas exchange in order to minimise any laser induced damage to the papillomacular bundle. A power setting was used which was just sufficient to produce a soft white burn in an area of attached retina and then applied in the distribution described above. This produced minimal or no reaction in the pigment epithelium underlying the detached retina at the time of application. There was no evident communication between the detachment and the vitreous cavity, and no attempt was made to drain subretinal fluid. The posterior segment was filled with 40% SF₆ in air.

Postoperatively the posterior retina was attached, but there was a collection of subretinal fluid inferiorly. It appeared that the previously submacular fluid had been displaced inferiorly by the gas bubble. This fluid was slowly absorbed over 16 weeks. At five months the retina was completely attached and the visual acuity had improved to 6/60 (Fig 2).

Discussion

An association between optic disc pit and macular



Figure 1 Preoperative fundus photograph. Arrow indicates optic disc pit.

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detachment is well recognised. Sugar¹ notes that macular lesions have been described in 51 of 157 cases of optic disc pit. Gass² in a study of five case reports suggests that serous detachment of the retina extending from the optic disc pit into the macular area is the basic lesion and that cystic retinal degeneration, macular hole formation, and retinal pigment epithelial disturbances are all secondary to the fluid which gains entrance to the subretinal space. Similar findings with the morning glory disc abnormality have led to suggestions that these two conditions are merely variations of the same basic abnormality.³

The origin of the subretinal fluid has aroused further interest, and the vitreous, subarachnoid space, inflammatory processes, abnormal blood vessels and orbital tissues have all been suggested as a source.³⁻⁶ Although internal traction has been implied as a mechanism associated with these detachments in several reports, there is only a single case report recording a retinal break as a contributing factor.⁷

The varied opinions on the origin of the subretinal fluid and consequent mechanisms underlying the associated retinal detachment have led to a wide range of reports on different approaches to management. In Gass's series of five patients² one underwent spontaneous resolution over 18 months without treatment. In the other four the macula remained detached despite three cases having treatment with either photocoagulation 'barrage' temporal to the pit or attempted alteration of the intraocular pressure. The results led Gass to state that either photocoagulation followed immediately by drainage of subretinal fluid or surgical decompression of the dural sheath of the optic nerve may prove to be more successful. Irvine *et al*³ describe such a case of optic nerve sheath fenestration in a previously vitrectomised eye with morning glory disc and macular detachment, observing gas from the fluid-gas exchange bubbling through the nerve sheath fenestration, confirming the communication between optic nerve and vitreous cavity.

In a study of 18 patients Abujamra *et al*⁸ treated 10 with photocoagulation and achieved full reattachment in only one case. Kapel *et al*⁹ reported on 14 patients with optic disc pit, eight of whom had an associated macular detachment and five were treated with argon laser, all unsuccessfully, and they concluded that no effective treatment was available for this serious complication.

There have been some more encouraging results. Kottow¹⁰ treated two patients with laser photocoagulation with successful reattachment

in both, though no information is given beyond two months and seven days respectively. Annesley *et al*¹¹ published a series of five cases of optic disc pit with macular detachment. In four cases successful reattachment was achieved with krypton laser alone, but three required more than one treatment session. The remaining patient underwent successful reattachment with krypton laser, vitrectomy, and fluid-gas exchange following two unsuccessful treatments with laser alone. Schatz and McDonald¹² treated five of six cases of optic disc pit with associated retinal detachment, two with laser photocoagulation alone and three combined with pars plana vitrectomy and fluid-gas exchange, all with eventual retinal reattachment. Von Fricken *et al*⁷ describe successful reattachment following vitrectomy and fluid-gas exchange in an unusual case of morning glory disc with rhegmatogenous retinal detachment.

This case report documents the successful reattachment of a serous macular detachment associated with optic disc pit by vitrectomy, endolaser, and fluid-gas exchange. The limited recovery in visual function is probably related to its longstanding nature and to the deposition of exudate on the posterior retinal surface and marked alteration in macular function characteristic of these detachments.² Further reports on the treatment of this uncommon condition are required so that clearer guidelines on management may be defined.

- 1 Sugar HS. Congenital pits in the optic disc and their equivalents (congenital colobomas and coloboma-like excavations) associated with submacular fluid. *Am J Ophthalmol* 1967; 63: 298-307.
- 2 Gass JDM. Serous detachment of the macula secondary to congenital pit of the optic nerve head. *Am J Ophthalmol* 1969; 67: 821-41.
- 3 Irvine AR, Brookes Crawford J, Sullivan J. The pathogenesis of retinal detachment with the morning glory disc and optic pit. *Retina* 1986; 6: 146-50.
- 4 Kindler P. Morning glory syndrome: unusual optic disc anomaly. *Am J Ophthalmol* 1970; 69: 376-84.
- 5 Hamada S, Ellsworth RM. Congenital retinal detachment and optic disk anomaly. *Am J Ophthalmol* 1971; 71: 460-4.
- 6 Adelung K, Aulhorn E, Thiel H-J. Functional disturbances associated with pitting of the optic disc. *Klin Monatsbl Augenheilkd* 1987; 191: 1-7.
- 7 von Fricken M, Dhungel R. Retinal detachment in the morning glory syndrome—pathogenesis and management. *Retina* 1984; 4: 97-9.
- 8 Abujamra S, De Souza EC, Da Cunha SL. Pitting of the optic disc. *Rev Bras Oftalmol* 1984; 43: 169-73.
- 9 Kapel J, Otrádel J, Dotrelova D. Maculopathies associated with congenital pits of the optic disc. *Czech Ophthalmol* 1983; 39: 9-17.
- 10 Kottow M. Photocoagulation of optic disc pits. *Ophthalmologica* 1982; 184: 26-9.
- 11 Annesley W, Brown G, Bolling J, Goldberg R, Fischer D. Treatment of retinal detachment with congenital optic pit by krypton laser photocoagulation. *Graefes Arch Clin Exp Ophthalmol* 1987; 225: 311-4.
- 12 Schatz H, McDonald R. Treatment of retinal detachment associated with optic nerve pit or coloboma. *Ophthalmology* 1988; 95: 178-86.

LETTERS TO THE EDITOR

Acute angle-closure glaucoma following botulinum toxin

SIR,—I would like to point out the great significance of the case report published by P Corridan *et al.*¹ They describe a patient who developed an acute angle-closure attack as a rare complication of periorcular botulinum toxin (BoTx) for blepharospasm.

As regards the pupillary effects of BoTx, it was Carl Kupfer² who first reported that retrobulbar injection of BoTx in rabbits produces mydriasis, probably by affecting the ciliary ganglion. However, very high doses were used in his study,² and in order to prevent lethal complications anti-BoTx antibodies were injected into all the animals. In contrast to the lethal doses used by Kupfer² we injected non-lethal doses of BoTx into the right orbit of rats (between 1.5 ng–2.5 ng BoTx). All animals developed ipsilateral mydriasis with cholinomimetic supersensitivity, without apparent optic nerve dysfunction.³ The mydriasis disappeared spontaneously over a period of eight weeks, and pupillary supersensitivity remained for longer. No electrophysiological evidence of generalised neuromuscular dysfunction followed the injected doses of 1.5–2.5 ng BoTx, which are close to those used in humans (0.25–6.5 units).⁴ Our conclusion is similar to that of Dr Kupfer's,² and we are also of the opinion that BoTx injected periorcularly or retrobulbarly diffuses towards the ciliary ganglion and there impedes the cholinergic innervation of the pupil.

This case report highlights a serious complication of periorcular BoTx injection, which, though rare, should be taken into consideration in patients with closable narrow angles who undergo this procedure.

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1 Corridan P, Nightingale S, Mashoudi N, Williams AC. Acute angle-closure glaucoma following botulinum toxin injection for blepharospasm. *Br J Ophthalmol* 1990; 74: 309–10.

2 Kupfer C. Selective block of synaptic transmission in ciliary ganglion by type A botulinum toxin in rabbits. *Proc Soc Exp Biol Med* 1958; 99: 474–6.

3 Levy Y, Kremer I, Shavit S, Korczyn AD. The pupillary effects of retrobulbar injection of botulinum toxin A (Oculinum) in albino rats. *Invest Ophthalmol Vis Sci* (In press).

4 Scott AB, Kennedy RA, Stubbs Jr HA. Botulinum A toxin injection as treatment for blepharospasm. *Arch Ophthalmol* 1985; 103: 347–50.

SIR,—In their recent case report of acute angle-closure glaucoma following botulinum toxin injection for blepharospasm¹ the authors recommend that patients at risk of developing angle-closure glaucoma should undergo prophylactic laser iridotomies. Laser iridotomy is the definitive treatment for most cases of angle-closure glaucoma, but it should not be performed without a proper indication. 'Prophylactic iridotomy' is a misleading term, because we tend to perform it in many eyes which will never develop a disease. Furthermore, one must bear in mind the possible complications of laser iridotomy, which include rare disasters such as foveal burns and retinal detachment, and less disastrous but more frequent compli-

cations such as transient or permanent elevation of the intraocular pressure – the latter due to pigment dispersion in the angle. In addition, there is considerable evidence that lens changes, leading to myopia and cataract, are frequent sequelae of laser iridotomy.²

There is an alternative to laser iridotomy in patients about to undergo botulinum toxin injection into the eyelids: why not prevent mydriasis by prescribing pilocarpine for a few days?

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1 Corridan P, Nightingale S, Mashoudi N, Williams AC. Acute angle-closure glaucoma following botulinum toxin injection for blepharospasm. *Br J Ophthalmol* 1990; 74: 309–10.

2 Hyams S. Angle-closure glaucoma. A comprehensive review of primary and secondary angle-closure glaucoma. Amsterdam: Kugler and Ghedini, 1990: 151–63.

SIR,—It is interesting that all the albino rats injected with botulinum toxin intraorbitally developed mydriasis, especially as the dose used by Drs Kremer and Levi was much lower than that used by Kupfer in 1958.

We thank Dr Hyams for his letter but would like to point out that we said in our paper, 'These who are at risk could have prophylactic YAG laser iridotomies.' We did not say they should have iridotomies. It would be inappropriate to be so didactic, as after all there are to date no other reports of angle-closure glaucoma following botulinum toxin injection periorcularly in humans. Regarding pilocarpine drops, they would need to be used for up to three months following each injection to coincide with the duration of action of botulinum toxin.

We would like to correct an error in our original paper regarding the dose of botulinum toxin used, in the paragraph entitled 'Technique.' The units were µg, not mg as stated. It should read 0.05 µg of freeze-dried botulinum toxin-haemagglutinin complex (0.008 µg neurotoxin).

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Lens biometry and diabetes

SIR,—In a study based on Scheimpflug photo evaluation of anterior segment structures early-onset diabetics have been compared with a control group.¹ Plots and regression lines are presented with biometry data as the dependent variable and age on the abscissa. Diabetics have thicker lenses (for age) than non-diabetics, a trend that is more apparent the longer the duration of the diabetes.

The authors state that this is the first report in which a precise assessment of the effect of 'true' diabetic duration on lens biometry has been possible. However, as part of a series of studies with focus on diabetic myopia we published a similar finding in 1987.² Compared to the present article our set-up was small-scale and with less detail regarding lens biometry. Our material was composed mainly of early-onset diabetics. A few type 2 diabetics with clinically clearly documented diabetes onset were included, our working hypothesis being the duration of the metabolic disorder proper, and not the insulin medication as focused on by Sparrow *et al.*

Whatever the mechanism, the two studies both support the concept of a positive cor-

relation between lens thickness and diabetes duration.

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1 Sparrow JM, Bron AJ, Brown NAP, Neil HAW. Biometry of the crystalline lens in early-onset diabetes. *Br J Ophthalmol* 1990; 74: 654–60.

2 Fledelius HC, Miyamoto K. Diabetic myopia – is it lens-induced? An oculometric study comprising ultrasound measurements. *Acta Ophthalmol (Kbh)* 1987; 65: 469–73.

SIR,—In our study of lens biometry in early-onset diabetes one of our objectives was to provide a precise statement concerning the effects on the lens of 'true' diabetic duration.¹ Information on disease duration of 'late-onset' diabetes is frequently inaccurate, and for this reason a strict definition of 'early onset' diabetes was applied in our study. Our information on 'true' diabetic duration was therefore reasonably precise.

Among the early-onset diabetics we found that, for all but one of the lens biometric features measured, age and diabetic duration were the most important determinants of lens biometry. In our multiple regression analysis we fixed the age slope in the diabetic subgroup to that of the non-diabetic control group prior to fitting the duration regression term. The slope of our duration term therefore represents the additional effect of diabetic duration over and above the normal aging effect. Our methods thus provide the most precise estimate available of the effect of 'true' diabetic duration on lens biometry.

Fledelius *et al* take issue with our statement that 'this report is the first in which a precise assessment of the effect of "true" diabetic duration on lens biometry has been possible.' In their paper, however, they provide no information regarding the diabetic type of the patients included in their study.² The reader is therefore left ignorant as to whether the 'true' diabetic duration of their patients was known. It is apparent only from their present communication that the patients in their study were mostly early-onset diabetics, with 'a few type 2 diabetics' included.

Fledelius *et al* employed a statistical method which demonstrated an effect of diabetic duration. Their method did not, however, provide 'a precise assessment of the effect of "true" diabetic duration on lens biometry.' In their method they calculated: 'individual lens thickness deviation values (in %), with + or – to signify higher or lower than expected according to non-diabetic regression line values for actual age and sex.' Using these calculated 'percentage deviation values' they then performed a second regression analysis against diabetic duration. Their method is acceptable for determining whether there is a duration effect or not, but it certainly has not provided 'a precise assessment of the effect of diabetic duration.' In fact, the regression coefficient quoted in their paper is a rather meaningless statistic, and does not provide the reader with any sort of useful estimate of the impact per year of diabetic duration on lens thickness. (Their reason for using a 'percentage deviation value' is unclear, as this would have the effect of distorting the magnitude of their duration effect, and implies an *a priori* belief that the impact of diabetic duration varies with the size of the lens.)

Our statement therefore is defensible, firstly, because no information regarding type of diabetes was provided by Fledelius *et al* in their paper,² and, secondly, because the

analysis employed by these authors did not provide 'a precise assessment of the effect of diabetic duration on lens biometry.' In terms of the diabetic subgroup the only similarity in the findings of these two studies was that they both demonstrated diabetic duration to be relevant to lens thickness.

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- 1 Sparrow JM, Bron AJ, Brown NAP, Neil HAW. Biometry of the crystalline lens in early-onset diabetes. *Br J Ophthalmol* 1990; 74: 654-60.
- 2 Fledelius HC, Miyamoto K. Diabetic myopia - Is it lens induced? An oculometric study comprising ultrasound measurements. *Acta Ophthalmol (Kbh)* 1987; 65: 469-73.

Hold-up of fluorescein in the arm

SIR,—A potentially common cause of early arterial phase fluorescein angiographic delay is reported. A fit 36-year-old draughtsman with unilateral paracentral visual distortion of six months' duration and bilateral macular retinal pigment epithelial changes was investigated by fluorescein angiography. 5 ml of 20% sodium fluorescein was injected by 21 gauge 'butterfly' into a dorsal hand vein, followed by 4 ml wash-through of 0.9% saline. No dye appeared in the retinal arterioles. The injected (upper) arm, resting on the fundus camera handlebar (fore-arm pronated), became uncomfortable above the elbow medially. This eased on lifting the limb. Fluorescein entered the retinal vessels 10 seconds thereafter (arm-retina circulation time¹), 117 seconds after initial intravenous injection. The delay was caused by the tourniquet effect of the camera handlebar.

The dorsal veins of the hand drain medially into the basilic vein and laterally into the cephalic vein, which may drain almost entirely into the basilic by a median vein in the cubital fossa.² Pressure on the medial upper arm in such individuals will slow venous drainage from the limb - not so if the proximal cephalic vein is larger.

In this patient the bolus effect was reduced, making identification of treatable leaking spots more difficult in the early phase angiograms. Upper limb position and support (previously described for antecubital injection³) must be considered during fluorescein angiography.

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- 1 David NJ, Saito Y, Heyman A. Diagnosis of carotid artery occlusion by arm to retina fluorescein appearance time. *Arch Neurol* 1961; 5: 165-70.
- 2 Williams PL, Warwick R, Dyson M, Bannister LH, eds. *Gray's anatomy*. Edinburgh: Churchill Livingstone, 1989: 806-7.
- 3 Rubinstein K. Arm-rest for fluorescein photography. *Br J Ophthalmol* 1968; 52: 864.

BOOK REVIEWS

Ophthalmology: What Shall I Do? By Jack J Kanski, Bev Daily. Pp 71. £5.95. Butterworth: Guildford, Surrey. 1989.

This slim book was written for general practitioners. It is the second in a series co-authored

by Dr Daily (the other covering neurology) and a very good buy at £5.95. Mr Kanski is well known for his books on many aspects of ophthalmology, all notable for their easily read text and high standards of production.

The text is set out as questions which are then answered in language which general practitioners will understand. The authors cover all common conditions such as senile macular degeneration, glaucoma, and cataract. In addition there are useful sections on less obvious topics such as visual standards and blind registration. There is a two-page display at the end entitled 'When to refer and to whom.' This sets out the rapidity of referral indicated for various conditions. The text is well set out on the pages, easily read, and impressively free of spelling mistakes. Illustrations are used sparingly but effectively.

The ophthalmic content is of a high standard. The text represents a distillation of modern views on clinical management of ophthalmic problems. There are a few points which ophthalmologists might be interested to discuss among themselves. For example, the reader is advised to remove a metal foreign body from the cornea in the surgery and clear the rust ring. Some may consider this unnecessarily exciting without the magnification of the slit-lamp. General practice elements are well covered - for example, the relationship between timolol and asthma, and the need for ophthalmologists to visualise senile macular changes before advising whether cataract surgery would be helpful. The index was particularly helpful in tracking items down.

This book really succeeds in two areas. First, it is short. This should encourage the potential reader to pick it up. The whole thing could be read in 10 minutes a day over seven days. Second, it offers solutions to problems general practitioners face during their daily work and is therefore much more 'user friendly' than a short textbook. The answers to clinical problems are given at a level which should not frighten anyone. A general practitioner who has struggled with conventional texts would probably find a few minutes with this book most enlightening. In conclusion we strongly recommend it for general practitioners.

JOHN BRAZIER
ROY MACGREGOR

Binocular Vision and Ocular Motility: Theory and Management of Strabismus. 4th Edn. By Gunter K von Noorden. Pp 557. £78. Mosby: Baltimore, 1990.

I am glad to welcome the latest edition of this classic textbook, the previous third edition having been published in 1985. Some changes have inevitably taken place. The title is no longer 'Burian and von Noorden's . . .', it is now entirely under the name of Professor von Noorden, but to make up for this there is now a picture of Dr Burian on the inside of the book, whereas previously we just had his name.

The third edition had 500 pages and 498 illustrations and the fourth edition has 557 pages with 504 illustrations. The main changes are that the chapter on neuroanatomy has been dropped, as the author feels that it is now impossible to give an adequate discussion of this subject in a book of this size and refers us very properly to Miller's edition of Walsh and Hoyt's textbook. To counterbalance this the chapter on sensory signs, symptoms, and adaptations has been substantially increased from 72 to 85 pages, and this is a considerable

benefit, as many textbooks do not go into as much detail in this area. In addition Professor von Noorden's recent interest in nystagmus is clearly reflected in the much enlarged section in the newer textbook.

I am glad to notice that Professor von Noorden now regards botulinum toxin injections as an adequate method of treatment of certain conditions, though he still seems to have his doubts as to its general applicability.

The surgical section has been reorganised, with new illustrations drawn by Rudolph Branner. I have to confess to a preference for the old illustrations. The Branner series, in my view, is too detailed and tends to have become much busier with many more pictures. For instance, in the previous edition it was possible to illustrate a rectus muscle resection in six pictures, though many of us would think that fewer would be adequate. The sequence now runs to 15 pictures, including pictures of the conjunctiva being sewn up. This seems to me an overabundance of visual material. Similar objections could be raised to all the other series of the surgical section of the book, and this is, I think, a retrograde step, though perhaps in North America it is of great value to show everything in a step-by-step fashion for the occasional surgeon.

I am glad to notice that the index now refers to anomalous correspondence and not anomalous retinal correspondence but puzzled as to why there are two page references to 'aileron' in the index. My dictionary defines these as devices for turning aeroplanes around, and I can find no actual reference to the word on the page to which we are referred.

In conclusion, however, I would emphasise that this is still in my view the very best single textbook on ocular motility and strabismus and that the chapter modifications are very much to its advantage. With the few quibbles about illustrations, this is yet again the book to be recommended to all persons with an interest in this area.

JOHN LEE

Glaucoma: A Colour Manual of Diagnosis and Treatment. By Jack J Kanski, James A McAllister. Pp 152. £45. Butterworth: Guildford, Surrey. 1989.

The ophthalmic subspecialties have given birth to a pantheon of learned texts, each filling a niche in the perceived requirements of the reading public. Some appear as atlases, others as multiauthored tomes held together by the editor, while others appear as the result of superhuman endeavour by a single author aiming to stamp his own personality on to his chosen field. Each of these 'types' share in common the central core of the subspecialty, embellished according to the author's perception of the niche to be filled. It is this core that Kanski and McAllister have captured.

In this slim volume, written in a clarity of style which the senior author has made his own, is summarised with admirable simplicity the whole of the subspecialty. Each chapter is well illustrated, with note form presentation of information and clinical pearls boxed for extra emphasis. A short bibliography for further reading is available for the curious. The book forms an admirable launch pad for the tyro and a worthwhile text for the paramedic. It is a text which any practitioner in the field would be proud to have produced but few could have achieved.

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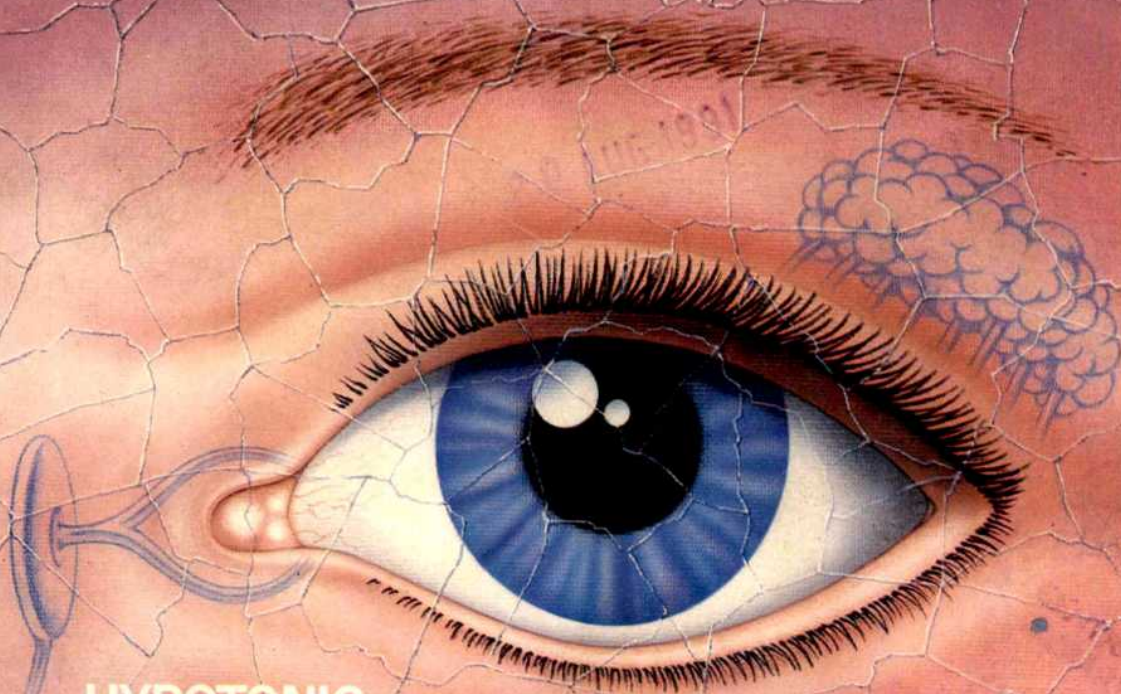


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